PORTO.
COMPREHENSIVE
CANCER CENTRE

RESEARCH REPORT
(2017)

IPOPORTO
INSTITUTO PORTUGUÊS DE ONCOLOGIA DO PORTO FG, EPE

PATIENT B3

PORTO.
COMPREHENSIVE
CANCER CENTRE

INSTITUTO DE INVESTIGAÇÃO
E INOVAÇÃO EM SAÚDE
UNIVERSIDADE DO PORTO

PORTO.
COMPREHENSIVE
CANCER CENTRE

RESEARCH REPORT

(2017)

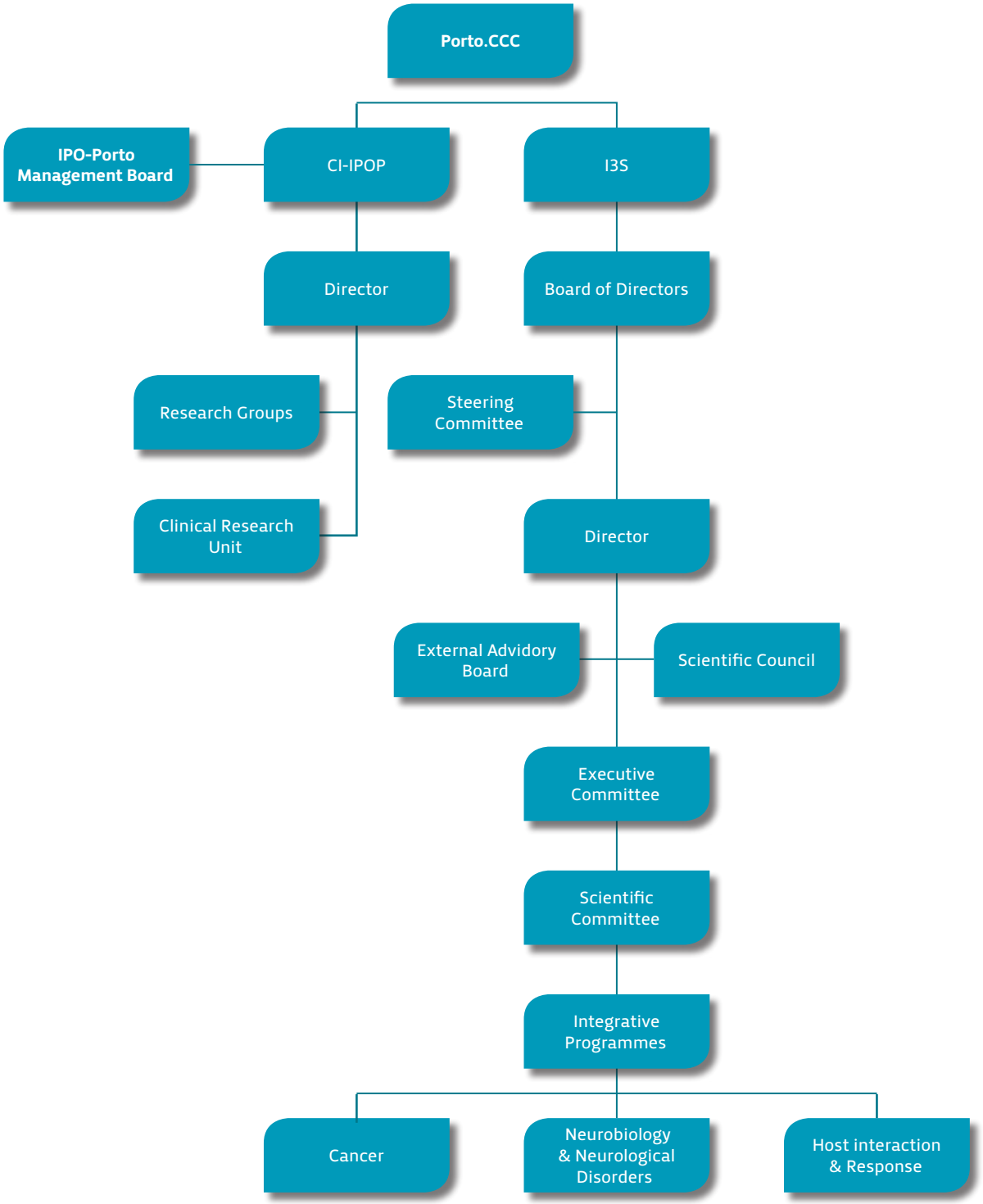
CONTENTS


Radioterapia

1

STRUCTURE & ORGANIZATION: RESEARCH UNITS


Radioterapia


Porto.CCC
IPO-Porto Management Board
CI-IPOP
I3S
Director
Board of Directors
Research Groups
Steering Committee
Clinical Research Unit
Director
External Advidory Board
Scientific Council
Executive Committee
Scientific Committee
Integrative Programmes
Cancer
Neurobiology & Neurological Disorders
Host interaction & Response


Omnifix

2

PORTO.CCC SCIENTIFIC EXTERNAL ADVISORY BOARD


Omnifix

From their start CI-IPOP and all the Institutes incorporated in I3S had Scientific Advisory Boards (composition below) with a similar way of action, according to recommendations from the Portuguese Science Foundation (FCT).

Recently a joint Board was appointed for I3S. This board is partly composed by members of individual institutes but also by new Board Members (composition below). In CI-IPOP and all Institutes there was an annual site visit and a report was issued with recommendations for the Institutes and for the groups. The reports from the CI-IPOP and I3S, available to Board Members before de site visit, guided the priorities for the local activities that included review of support facilities, interviews with group leaders, post-docs and PhD and Master student's.

- **Andrés J. García**, Woodruff School of Mechanical Engineering, Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, USA
- **Angel Carracedo**, University of Santiago de Compostela, Spain
- **Carlos Caldas**, Cancer Research UK Cambridge Research Institute, University of Cambridge, UK;
- **Christopher Leaver**, University of Oxford, Oxford, UK (chair)
- **David Huntsman**, Pathology and Laboratory Medicine and Obstetrics and Gynaecology at the University of British Columbia, Canada
- **Erich Nigg**, University of Basel, Switzerland
- **Felix Mitelman**, Clinical Genetics Department, Lund University, Sweden
- **Fernando Lopes da Silva**, Vrije Universiteit, Amesterdam, The Netherlands
- **Fred Bosman**, Université de Lausanne, Switzerland
- **Gerrit A. Meijer**, Netherlands Cancer Institute, Amsterdam, The Netherlands
- **Grabriel Capellá**, Catalan Institute of Oncology, Barcelona, Spain
- **Ivan Damjanov**, University of Kansas, USA
- **Jacques Neefjes**, The Netherlands Cancer Institute, Amsterdam, The Netherlands
- **James Fawcett**, Cambridge Centre for Brain Repair, Cambridge, UK
- **James Kirkpatrick**, Institute of Pathology, Johannes Gutenberg University, Mainz, Germany
- **Jean Marc Egly**, Institute de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, France
- **Jean-Pierre Gorvel**, Centre d'Immunologie de Marseille-Luminy, France
- **Jim Malone**, Trinity College, St. James Hospital, Irelang
- **Josep Planell**, Centro de Investigación en Ingeniería Biomédica (CREB), ETSEIB, Barcelona, Spain
- **Marc Mareel**, Universiteit Gent, Belgium
- **Marianne G. Rots**, University Medical Center Groninge, The Netherlands
- **Nuria Verdaguer**, Instituto de Biologia Molecular de Barcelona, Barcelona, Spain
- **Peter Heutink**, Vrije Universiteit, Amsterdam, The Netherlands
- **Reinhard Faessler**, Max Planck Institute of Biochemistry, Germany

3

ONCOLOGY RESEARCH STRATEGY PLAN

CI-IPOP was officially established in September 15, 2003, and is hosted by the Instituto Português de Oncologia do Porto Francisco Gentil (hereafter IPO-Porto), the largest specialized Portuguese cancer institution with a staff number of about 1.800 and more than 10.000 new patients per year that has a triple role: (1) patient care, (2) research, and (3) education in Oncology. IPO-Porto is a leading institution in treating patients with cancer and precancerous lesions, and this excellence in patients care is rooted in a strong enforcement in research. CI-IPOP includes currently five research groups working on translational cancer research, all having a high intensity laboratory level. Furthermore, CI-IPOP included a Clinical Research Unit and a number of clinical staff that publishes regularly.

CI-IPOP has the mission to promote translational scientific activity in Oncology and its main objective is the understanding of the pathobiologic mechanisms underlying the development of cancer, enabling prevention, early diagnosis, accurate prognostic evaluation, and development of more effective therapies.

CI-IPOP was formally recognized by the Science and Technology Foundation, the governmental agency that manages scientific and technological activities in Portugal, as an R&D Unit in 2004 and it was classified as "Very Good" in its last external evaluation (2015).

IPATIMUP was created in 1989 under the auspices of the University of Porto as a Non-Profit Private Association of Public Utility, mainly devoted to cancer research. Since 2000, IPATIMUP is also an Associated Laboratory in Health Sciences of the Ministry of Science and Technology of Portugal. IPATIMUP aims are: (1) To be a leading health science research institution through internationally competitive science on molecular pathology and molecular and population genetics. (2)To serve society through science by directing discoveries to the improvement of cancer prevention and management of cancer patients, and through communicating the significance of the Institution's findings to the public. (3)To enjoy a reputation for doing good translational research and for providing appropriate training conditions, i.e., for successfully translating good science into good clinical practice and for ensuring good advanced training. (4) As an Associated Laboratory, the IPATIMUP collaborates with the Government in health and wealth creation, quality of life and public awareness of Science.

In 2014 a Consortium - I3S – resulted from the joined forces of IPATIMUP and two other research Institutes from Porto: INEB, founded in 1989, devoted to promoting research, advanced training and technology transfer in Biomedical Engineering, and IBMC, founded in 1997 and devoted to research in Life Sciences. Both Institutes are leading scientific organizations, internationally acknowledged in their areas of expertise. The I3S was evaluated in 2015 and rated as "Exceptional", obtaining the highest score and the highest financing among all research institutions in Portugal.

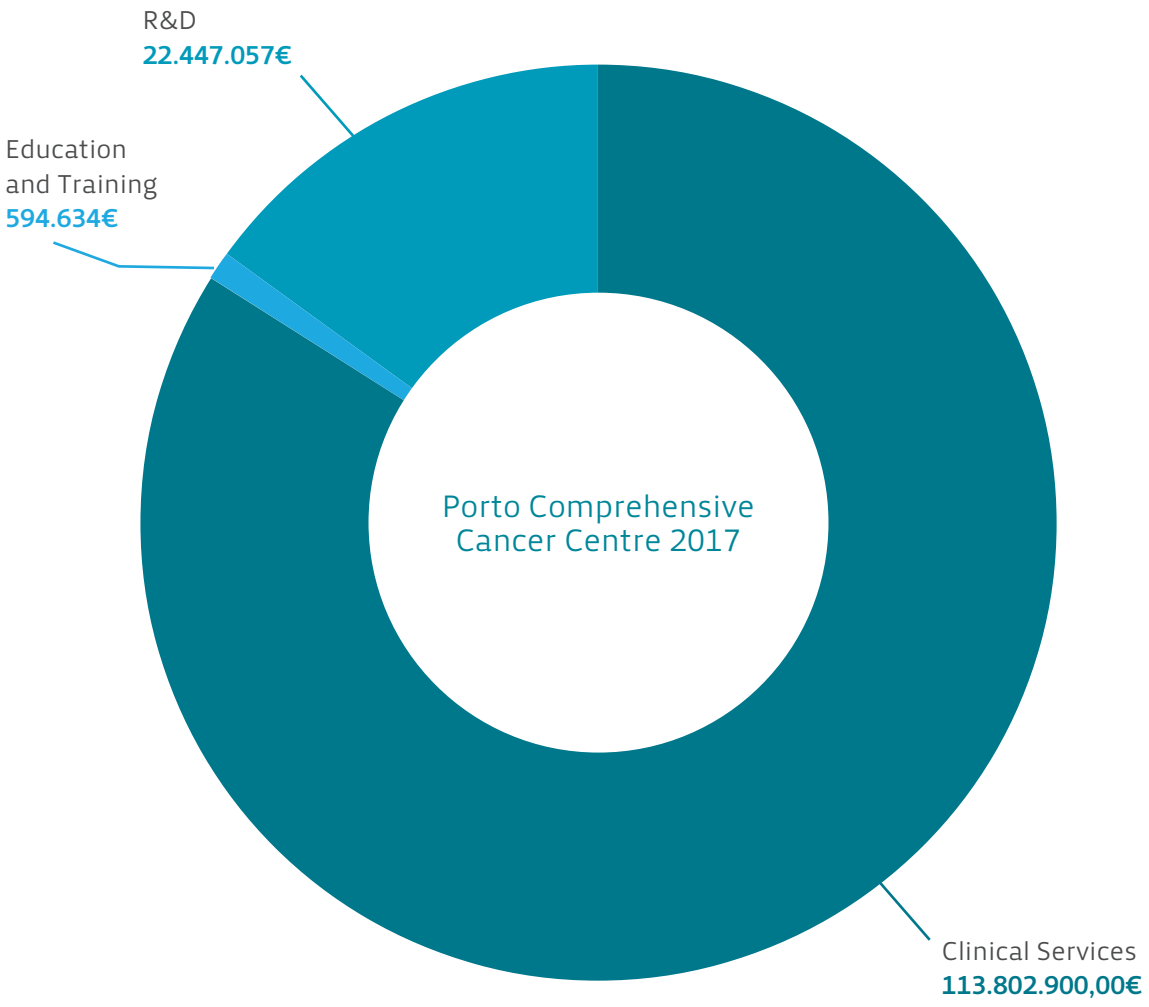
Together with IPO-Porto, a renovated **Porto Comprehensive Cancer Centre – Porto.CCC** – was established in a recent agreement signed in 2017, under the auspices of the Ministry of Health and the Ministry of Science and Technology. At this stage, the aggregation of INEB and IBMC to the Porto.CCC will add relevant research on biomaterials and basic research, most importantly a strong group in the biology of cell division. This further step boosts the critical mass both at the translational and the basic research level. **Porto.CCC** is from the very first day the major player in cancer research in Portugal and also, in some of its areas of expertise, a major player at the European level. The Porto.CCC joins together two institutions coming from the Ministry of Health (IPO-Porto) and the Ministry of Science and Technology (I3S) integrating basic, pre-clinical and clinical research, creating a regional platform that, in the long run, will reinforce the role that these institutions already play at the national level. As a start, IPO-Porto and IPATIMUP were instrumental in the creation, in 2013, of the Portuguese Association for Cancer Research (ASPIC) that connects cancer researchers from all scientific areas and is affiliated to EACR. This initiative showed the ability of **Porto.CCC** to launch a nationwide cancer program.

Porto.CCC will help to create an environment where differences in the activities of clinical and basic researchers will be harmonized, facilitating the entry of MDs in the scientific environment and providing the tools for clinicians to access research facilities and expertise usually segregated in institutions that live apart. Access to funding at national and international levels will be boosted and education and training of young researchers, both clinical and basic, will benefit from an environment where the biology underlying patient's treatment can be understood and where basic research will be challenged to translate discoveries into the clinic. The culture on the move is to have all participating in the international endeavor to increase preventive attitudes, to improve early diagnosis, to better stratify patients for treatment options of today and tomorrow, in brief, to meet the grand challenge of dealing with cancer every day in a better way for patients benefit.

4

GLOBAL BUDGET (2017)

Porto Comprehensive Cancer Centre	2017
Clinical Services	113.802.900,00€
Education and Training	594.634,03€
R&D	22.447.057,00€
Global Budget	**136.844.591,03 €**

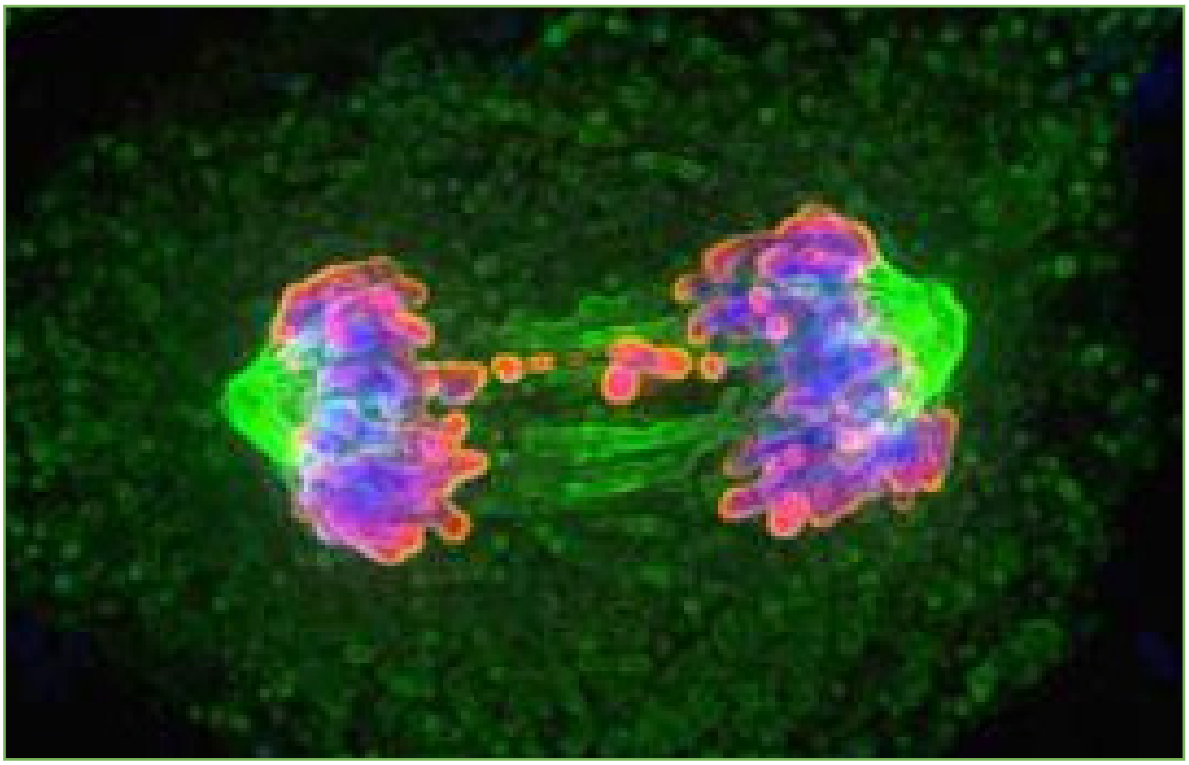


5

RESEARCH GROUPS

AGEING AND ANEUPLOIDY

GROUP LEADER: **Elsa Logarinho**



AIM OF THE GROUP

Ageing is a biological process characterized by the progressive deterioration of physiological functions known to be the main risk factor for chronic diseases including cancer. Given the exponential increase of the elderly population and its substantial burden on the health care system, the research in ageing biology becomes a priority.

There has been an emerging connection between ageing and aneuploidy, an aberrant number of chromosomes, which is a cancer hallmark.

Our group, Aging and Aneuploidy, has been studying the molecular mechanisms behind age-associated aneuploidy and exploring their implications in cancer and ageing therapies.

MAJOR ACHIEVEMENTS IN 2016

Macedo JC, Vaz S, Logarinho E. Mitotic dysfunction associated with aging hallmarks. Advances in Experimental Medicine and Biology 1002:153-188, 2017. [Book Series: Chapter] DOI: 10.1007/978-3-319-57127-0_7
There has been an emerging connection between aging and aneuploidy, an aberrant number of chromosomes, even though the molecular mechanisms behind age-associated aneuploidy remain largely unknown. In recent years, several genetic pathways and biochemical processes controlling the rate of aging have been identified and proposed as aging hallmarks. Primary hallmarks that cause the accumulation of cellular dam-

age include genomic instability, telomere attrition, epigenetic alterations and loss of proteostasis. We reviewed the provocative link between these aging hallmarks and the loss of chromosome segregation fidelity during cell division, which could support the correlation between aging and aneuploidy seen over the past decades. Secondly, we reviewed the systemic impacts of aneuploidy in cell physiology and emphasize how these include some of the primary hallmarks of aging. Based on the evidence, we proposed a mutual causality between aging and aneuploidy.

Macedo JC, Vaz S, Bakker B, Ribeiro R, Bakker P, Escandell JM, Ferreira MG, Medema RH, Foijer F, Logarinho E (2018). Molecular basis of mitotic decline during human aging. BioRxiv 261008; doi.org/10.1101/261008.
Macedo JC, Vaz S, Bakker B, Ribeiro R, Bakker P, Escandell JM, Ferreira MG, Medema RH, Foijer F, Logarinho E (2018). FoxM1 repression during human aging leads to mitotic decline and aneuploidy-driven full senescence. Nature Communications (in press).
Here we show, through direct live-cell imaging of young, middle-aged, and old-aged primary human dermal fibroblasts, that aneuploidy increases with aging due to general dysfunction of the mitotic machinery. Increased chromosome mis-segregation in elderly mitotic cells correlates with an early senescence-associated secretory phenotype (SASP) and repression of Forkhead box M1 (FoxM1), the transcription factor that drives G2/M gene expression. FoxM1 induction in elderly and Hutchison-Gilford Progeria Syndrome fibroblasts prevents aneuploidy and, importantly, ameliorates cellular aging phenotypes. Moreover, we show that senescent fibroblasts isolated from elderly donors' cultures are often aneuploid, and that aneuploidy is a key trigger into full senescence phenotypes. Based on this feedback loop between cellular aging and aneuploidy, we propose modulation of mitotic efficiency through FoxM1 as a potential strategy against aging and progeria syndromes.

Shukla S, Milewski D, Pradhan A, Rama N, Rice K, Le T, Flick MJ, Vaz S, Zhao X, Setchell KD, Logarinho E, Kalinichenko VV, Kalin TV (2018). FoxM1 inhibitor RCM-1 decreases carcinogenesis and nuclear β-catenin. Molecular Cancer Therapeutics (submitted).
The oncogenic transcription factor FOXM1 has been previously shown to play a critical role in carcinogenesis by inducing cellular proliferation in multiple cancer types. A small molecule compound, RCM-1, has been recently identified from high throughput screen as an inhibitor of FOXM1 in vitro and in mouse model of allergen-mediated lung inflammation. In the present study, we examined anti-tumor activities of RCM-1 using tumor models. Treatment with RCM-1 inhibited tumor cell proliferation concordant with inhibition of FOXM1 nuclear localization in these cells. RCM-1 reduced the incidence and growth of tumor cell colonies in the colony formation assay. In animal models, RCM-1 treatment inhibited growth of mouse rhabdomyosarcoma Rd76-9, melanoma B16-F10 and human H2122 lung adenocarcinoma. RCM-1 decreased FOXM1 protein in the tumors, reduced tumor cell proliferation and increased tumor cell apoptosis. RCM-1 decreased protein levels and nuclear localization of β-catenin, and inhibited protein-protein interaction between β-catenin and FOXM1 in cultured tumor cells and in vivo. Altogether, our study provides important evidence of anti-tumor potential of the small molecule compound RCM-1, suggesting that RCM-1 can be a promising candidate for anti-cancer therapy.

Cimino M, Gonçalves RM, Bauman E, Barroso-Vilares M, Logarinho E, Barrias CC, Martins MCL. Optimization of the use of a pharmaceutical grade xeno-free medium for in vitro expansion of human mesenchymal stem/stromal cells. J Tissue Eng Regen Med. 2018 Mar;12(3):e1785-e1795. doi: 10.1002/term.2588. Epub 2017 Dec 25.
Human bone marrow-derived mesenchymal stem/stromal cells (hMSCs) are considered promising therapeutic agents in the field of cell therapy and regenerative medicine. Most of the protocols for hMSCs in vitro culture use foetal bovine serum as medium supplement that, being from animal origin, presents several safety concerns and may initiate xenogeneic immune responses after cells transplantation. This work reports the optimization of a pharmaceutical-grade xeno-free strategy for hMSCs in vitro expansion based on the supple-

mentation of basal medium with a pharmaceutical-grade human plasma-derived supplement for cell culture (SCC) and 2 human growth factors (bFGF and TGFβ1), plus a coating of human plasma fibronectin (Fn). hMSCs expanded in SCC-based formulation maintained their phenotype and differentiation capacity into osteogenic, adipogenic, and chondrogenic lineages, without alterations in cell karyotype.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

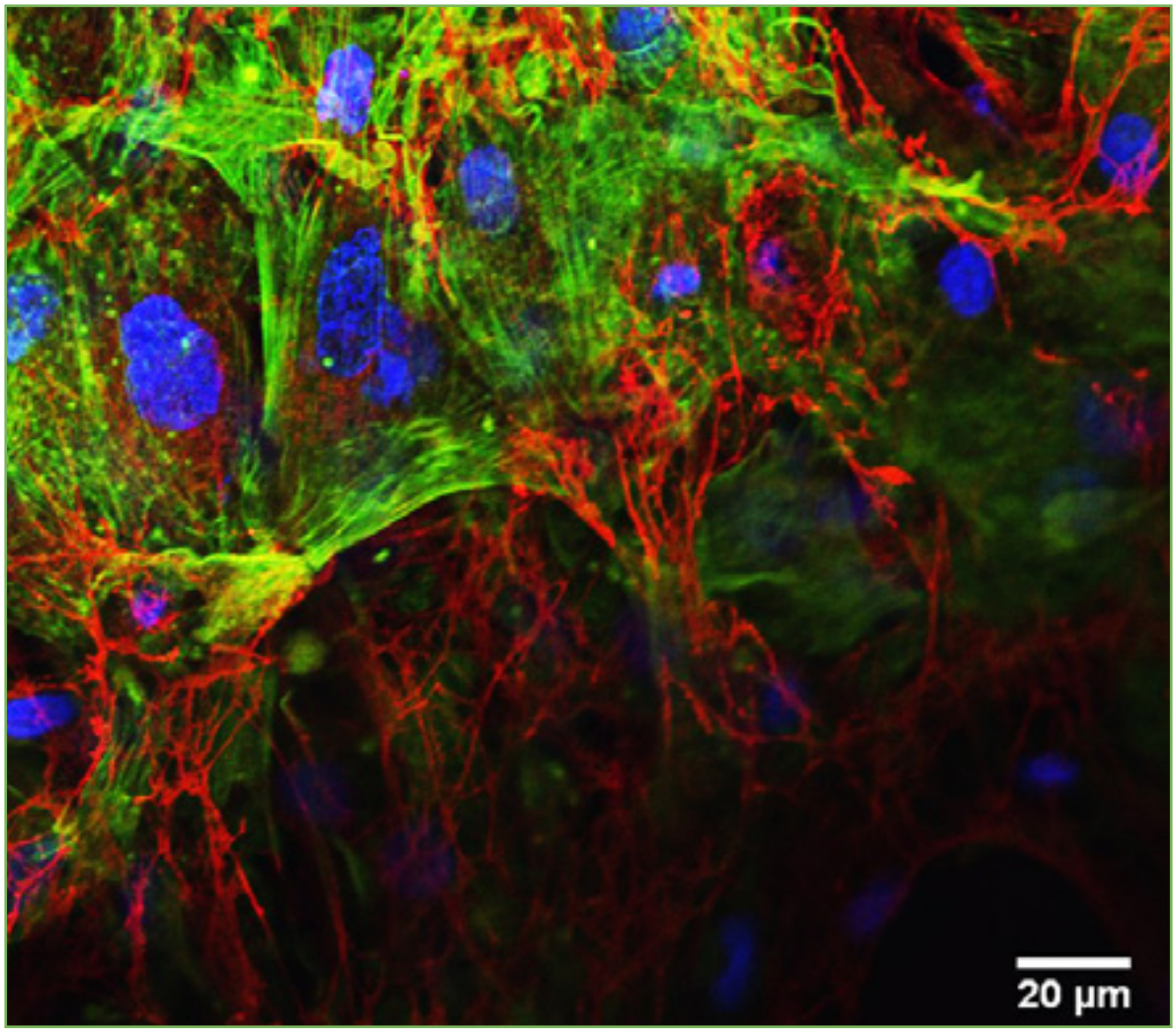
1. Macedo, JC, Vaz, S and Logarinho, E. Mitotic Dysfunction Associated with Aging Hallmarks. Advances in experimental medicine and biology. 2017;1002:153-88 https://www.ncbi.nlm.nih.gov/pubmed/28600786 (Impact facotr: 1.76)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Rita Sousa Castro	MSc	Employed	Research Assistant	100
Elsa Logarinho	PhD	Employed	Principal Researcher	100
Fábio Júnior Verissimo Ferreira	MSc	FCT Fellowship	PhD student	100
Joana Catarina Macedo	BSc	NA	PhD student	100
Monika Barroso Vilares	MSc	BIM Fellowship Norte2020CANCER15	Research Trainee	100
Rui Sérgio Ribeiro	MSc	FCT Fellowship	PhD student	100
Sara Marisa Duarte Vaz	MSc	FCT Fellowship SFRH/BD/125017/2016	PhD student	100
Sofia Melo Pereira	PhD	Fellowship	PostDoc	100

BIOMATERIALS FOR MULTISTAGE DRUG AND CELL DELIVERY (BIOCARRIER)

GROUP LEADER: **Pedro L. Granja**



AIM OF THE GROUP

The group has specialized in directing and mechanistically following cell behavior in engineered 3D microenvironments toward the development of cell-instructive biomaterials for tissue regeneration. Hydrogels were functionalized with cell-interactive peptides in order to reproduce some essential features of the extracellular matrix, namely cell adhesion, proteolytic degradation and guided cell differentiation. They are being investigated as models to study cell behavior in 3D conditions in regenerative therapies (bone, vascular and skin) and degenerative conditions (cancer). Biofunctionalized nanoparticulate systems are also being investigated with application in the pharmaceutical and biomedical fields, to provide the controlled and targeted delivery of bioactive molecules in therapies for infectious diseases (e.g. HIV) and cancer, as well as diagnosis (e.g. cancer)namely by the discovery of new specific biomarkers for gastric cancer, namely CD44v6.

MAJOR ACHIEVEMENTS IN 2017

We have developed **i)** new formulations of cell instructive/responsive hydrogels, to be used as 3D artificial matrices; **ii)** new formulations of biuoinks to bioprinted cellularized tissue-engineered 3D constructs; **iii)** several types of cellularized 3D constructs for tissue engineering, combining various cell types and/or structures (hybrid materials), using biofunctional hydrogels and emergent processing technologies (bioprinting and electrospinning); **iv)** new systems (targeted nanoparticles) for nanomedicine applications; **v)** new bioengineered 3D models that provide a powerful tool to investigate the role of the microenvironment, particularly the extracellular matrix, on cancer progression.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Cimino, M, Goncalves, RM, Barrias, CC and Martins, MCL. Xeno-Free Strategies for Safe Human Mesenchymal Stem/Stromal Cell Expansion: Supplements and Coatings. Stem cells international. 2017;2017:6597815 https://www.ncbi.nlm.nih.gov/pubmed/29158740 (Impact Factor: 3.989)
2. Henriques Lourenco, A, Neves, N, Ribeiro-Machado, C, Sousa, SR, Lamghari, M, Barrias, CC, Trigo Cabral, A, Barbosa, MA and Ribeiro, CC. Injectable hybrid system for strontium local delivery promotes bone regeneration in a rat critical-sized defect model. Scientific reports. 2017;7(1):5098 https://www.ncbi.nlm.nih.gov/pubmed/28698571 (Impact Factor: 4.122)
3. Pinto, ML, Rios, E, Silva, AC, Neves, SC, Caires, HR, Pinto, AT, Duraes, C, Carvalho, FA, Cardoso, AP, Santos, NC, Barrias, CC, Nascimento, DS, Pinto-do, OP, Barbosa, MA, Carneiro, F and Oliveira, MJ. Decellularized human colorectal cancer matrices polarize macrophages towards an anti-inflammatory phenotype promoting cancer cell invasion via CCL18. Biomaterials. 2017;124:211-24 https://www.ncbi.nlm.nih.gov/pubmed/28209528 (Impact Factor: 8.806)
4. Leite, JP, Mota, R, Durao, J, Neves, SC, Barrias, CC, Tamagnini, P and Gales, L. Cyanobacterium-Derived Extracellular Carbohydrate Polymer for the Controlled Delivery of Functional Proteins. Macromolecular bioscience. 2017;17(2) https://www.ncbi.nlm.nih.gov/pubmed/27594050 (Impact Factor: 3.392)
5. Dias, JR, Baptista-Silva, S, Oliveira, CMTd, Sousa, A, Oliveira, AL, Bártolo, PJ and Granja, PL. In situ crosslinked electrospun gelatin nanofibers for skin regeneration. European Polymer Journal. 2017;95:161-73 http://www.sciencedirect.com/science/article/pii/S0014305717306237 (Impact Factor: 3.741)
6. Pereira, RF, Sousa, A, Barrias, CC, Bayat, A, Granja, PL and Bártolo, PJ. Advances in bioprinted cell-laden hydrogels for skin tissue engineering. Biomanufacturing Reviews. 2017;2(1):1 https://doi.org/10.1007/s40898-017-0003-8 (Impact Factor: NA)
7. Costa-Almeida, R, Carvalho, DT, Ferreira, MJ, Pesqueira, T, Monici, M, van Loon, JJ, Granja, PL and Gomes, ME. Simulated hypergravity induces changes in human tendon-derived cells: From cell morphology to gene expression. 2017 http://repositorium.sdum.uminho.pt/bitstream/1822/47081/1/19138-P100-944_Part330_achilles.pdf (Impact Factor: NA)
8. Bauleth-Ramos, T, Shahbazi, M-A, Liu, D, Fontana, F, Correia, A, Figueiredo, P, Zhang, H, Martins, JP, Hirvonen, JT, Granja, P, Sarmento, B and Santos, HA. Nutlin-3a and Cytokine Co-loaded Spermine-Modified Acetalated Dextran Nanoparticles for Cancer Chemo-Immunotherapy. Advanced Functional Materials. 2017;27(42):1703303 https://onlinelibrary.wiley.com/doi/abs/10.1002/adfm.201703303 (Impact Factor: 13.325)
9. Silva, ED, Babo, PS, Costa-Almeida, R, Domingues, RMA, Mendes, BB, Paz, E, Freitas, P, Rodrigues, MT, Granja, PL and Gomes, ME. Multifunctional magnetic-responsive hydrogels to engineer tendon-to-bone interface. Nanomedicine : nanotechnology, biology, and medicine. 2017 https://www.ncbi.nlm.nih.gov/pubmed/28614734 (Impact Factor: 6.500)
10. Kennedy, PJ, Oliveira, C, Granja, PL and Sarmento, B. Antibodies and associates: Partners in targeted drug delivery. Pharmacol Ther. 2017;177:129-45 https://www.ncbi.nlm.nih.gov/pubmed/28315359 (Impact Factor: 10.376)
11. Neves, MI, Wechsler, ME, Gomes, ME, Reis, RL, Granja, PL and Peppas, NA. Molecularly Imprinted Intelligent Scaffolds for Tissue Engineering Applications. Tissue engineering. Part B, Reviews. 2017;23(1):27-43 https://www.ncbi.nlm.nih.gov/pubmed/27484808 (Impact Factor: 3.508)
12. Araújo, F, das Neves, J, Martins, JP, Granja, PL, Santos, HA and Sarmento, B. Functionalized materials for multistage platforms in the oral delivery of biopharmaceuticals. Progress in Materials Science. 2017;89:306-44 http://www.sciencedirect.com/science/article/pii/S0079642517300567 (Impact Factor: 23.750)

13. Dias, JR, Dos Santos, C, Horta, J, Granja, PL and Bartolo, PJDS. A new design of an electrospinning apparatus for tissue engineering applications. International Journal of Bioprinting. 2017;3(2):9 http://ijb.whioce.com/index.php/int-j-bioprinting/article/view/109 (Impact Factor: NA)

Books & Book Chapters

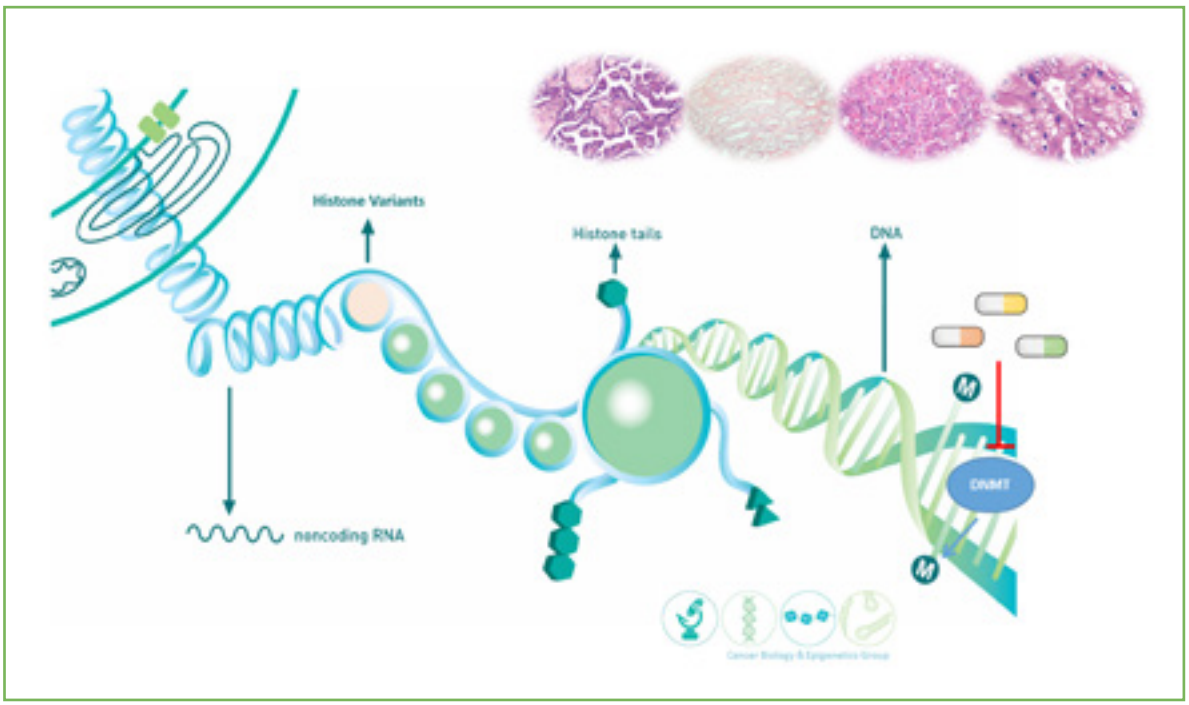
1. Sousa, A, Neves, SC, Gonçalves, IC and Barrias, CC. In vitro interaction of polymeric biomaterials with cells. In: M. C. Tanzi and S. Farè, editors. Characterization of Polymeric Biomaterials: Woodhead Publishing; 2017. p. 285-315 http://www.sciencedirect.com/science/article/pii/B9780081007372000121

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Castro	BSs		MSc student	
Ana Garizo	MSc		PhD student	
Ana Luísa Torres	MSc		PhD student	
Aureliana Sousa	PhD		Assistant Researcher	
Bianca Lourenço	MSc		PhD student	
Carlos Diogo	BSc		MSc student	
Carolina Paredes	BSc		MSc student	
Cristina Barrias	PhD		Principal Researcher	
Daniel Ferreira	MSc		PhD student	
Eduardo Capitão	MSc		MSc student	
Filipa Teixeira	BSc		MSc student	
Isobel Taylor	MSc		PhD student	
Juliana Dias	MSc		PhD student	
Manuel Barros	MSc		Research Fellowship	
Marco Araújo	PhD		Post-Doc Researcher	
Mariana Neves	MSc		PhD student	
Patricia Silva	MSc		PhD student	
Pedro Alves	BSc		MSc student	
Pedro L. Granja	PhD		Principal Researcher	
Rúben Pereira	MSc		PhD student	
Samuel José	BSc		MSc student	
Sara C. Neves	MSc		PhD student	
Sílvia Lourenço	PhD		Post-Doc Researcher	
Tália Figueiredo	PhD		Post-Doc Researcher	
Tiago Santos	PhD		PhD fellow	

CANCER BIOLOGY & EPIGENETICS

GROUP LEADER: **Carmen Jerónimo**



AIM OF THE GROUP

The long-term core goal of the Cancer Biology and Epigenetics Group (CBE) is to portray the epigenetic mechanisms involved in the genesis of urological cancers. Recently, we have been tackling the contribution of deregulated non-coding RNAs expression and its interaction with other epigenetic mechanisms that may induce/promote malignant transformation.

Specifically, within the framework of Precision Medicine, we have ongoing four major lines of investigation:

(1) Using body fluids - liquid biopsies (plasma or serum) and urine - for detecting cell-free tumor-specific epigenetic biomarkers (methylated DNA or noncoding RNA) we aim at developing new cancer biomarkers for screening/ detection and to assist in patient's clinical management. We have identified several putative markers in tissues of the four major human malignancies [those of breast (BrCa), prostate (PCa), colorectal (CRC) and lung (LCa)] as well in other urological cancers [bladder (BlCa), kidney (KCa) and testicular germ-cell tumors (TGCT)] that are already being tested in body fluids (Costa-Pinheiro, Epigenomics 2015, Costa AL, epigenomics 2017).

(2) Due to the heterogeneous biology of PCa, only a limited proportion of tumors are deemed to be clinically significant. Because non-coding protein genes / non-coding RNA aberrations, particularly, long non-coding RNAs have been recently implicated in PCa carcinogenesis (Ramalho-Carvalho, CRM, 2017) we plan to focus our research to better understand their role in molecular pathways associated with PCa aggressiveness, AR

and PTEN signaling pathways. Moreover, since long noncoding RNA (lncRNA) are target by also target by internal chemical modifications, such as N6-methyladenosine (m6A), that may impact in various cellular processes, through post-transcriptional regulation of gene expression (Fu, NRG 2014 & Roundtree, cell 2017) we will attempt to discover their role in PCa onset. Thus, it is likely then that unravelling the biological functions of ncRNAs in PCa will provide new insights into their functions, mechanisms of action, and potential usefulness as tools for PCa management.

(3) Despite nephrectomy is performed with curative intent, approximately 30% of patients with localized clear cell Renal Cell Carcinoma (ccRCC), develop metastases and perish due to this malignancy. Herein, we intend to discover Long non-coding RNAs (LnCRNAs) that might regulate Von Hippel-Lindau Pathway and its implication in metastization.

(4) Furthermore, in the same context of Precision Medicine, we are investigating the potential of epigenetic modulators (e.g., DNA methyltransferase and histone deacetylases inhibitors) for cancer therapy, through manipulation of cell lines, characterizing their biological effects and antineoplastic capabilities. Owing to the relevance that Immuno-oncology has demonstrated in recent years, we are also investigating the epigenetic modulation of expression of biomolecules involved in immune checkpoint regulation, aiming at the improvement of immunotherapeutic strategies by combination with epi-drugs.

MAJOR ACHIEVEMENTS IN 2017

Epigenetic disruption of miR-130a promotes prostate cancer by targeting SEC23B and DEPDC1. Cancer Lett 385:150-159, 2017.

Downregulation of miR-130b~301b cluster is mediated by aberrant promoter methylation and impairs cellular senescence in prostate cancer.

Genome-wide screening technologies have revolutionized our understanding of the genetic and epigenetic landscape of prostate cancer (PCa). Because only a few somatically altered genes have been consistently implicated in prostate carcinogenesis we focused on the discovery of new epigenetic aberrations. We showed that PCa foci contain aberrant methylation in a large number of non-coding genes involved in molecular pathways implicated in the development of PCa. This led to the recent identification of epigenetically-regulated microRNAs (miR-130a and miR-130b~301b cluster) targeting oncogenes involved in several molecular pathways that determine malignancy features of PCa. These findings support the use of mechanism-based therapies for personalized patient care.

MiR-193b promoter methylation accurately detects prostate cancer in urine sediments and miR-34b/c or miR-129-2 promoter methylation define subsets of clinically aggressive tumors.

Due to the heterogeneous biology of PCa, only a limited proportion of tumors are deemed to be clinically significant. Thus, there is an unmet need for tools that may predict which cancers should be immediately treated and which may be safely referred to active surveillance. In advanced PCa, in particular in castration-resistant disease, it is also pivotal to determine which treatment might be more effective for each patient. We have discovered a panel of microRNas that are able to accurately detect PCa in liquid biopsies and simultaneously identify a patients' subset harbouring clinically significant PCa, independently of standard clinicopathological parameters.

MicroRNA promoter methylation: a new tool for accurate detection of urothelial carcinoma.

Herein we proposed the aberrant promoter methylation of a panel of newly identified non-coding genes as a non-invasive test for detecting urothelial cancer (both upper urinary tract and bladder cancer).

Identification of clear cell renal cell carcinoma and oncocytoma using a three-gene promoter methylation panel. With this study, we demonstrated that a panel including OXR1 and MST1R promoter methylation allows for specific and sensitive identification of renal cell tumors, and, especially, of clear cell renal cell carcinoma. Moreover, higher OXR1 promoter methylation levels associated with clear cell renal cell carcinoma nuclear grade, a surrogate for tumor aggressiveness. Thus, gene promoter methylation analysis might be used as an ancillary tool in diagnostic management of renal masses.

Overall, our more recent findings confirm the biological and clinical relevance of epigenetic alterations in Urological tumors, setting the stage for the development of novel biomarkers to assist in patient's clinical management.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Arthurs, C, Murtaza, BN, Thomson, C, Dickens, K, Henrique, R, Patel, HRH, Beltran, M, Millar, M, Thrasivoulou, C and Ahmed, A. Expression of ribosomal proteins in normal and cancerous human prostate tissue. PloS one. 2017;12(10):e0186047 https://www.ncbi.nlm.nih.gov/pubmed/29016636 (Impact Factor: 2.766)
2. Barbosa, J, Faria, J, Leal, S, Afonso, LP, Lobo, J, Queiros, O, Moreira, R, Carvalho, F and Dinis-Oliveira, RJ. Acute administration of tramadol and tapentadol at effective analgesic and maximum tolerated doses causes hepato- and nephrotoxic effects in Wistar rats. Toxicology. 2017;389:118-29 https://www.ncbi.nlm.nih.gov/pubmed/28689766 (Impact Factor: 3.265)
3. Bartosch, C, Afonso, M, Pires-Luis, AS, Galaghar, A, Guimaraes, M, Antunes, L and Lopes, JM. Distant Metastases in Uterine Leiomyosarcomas: The Wide Variety of Body Sites and Time Intervals to Metastatic Relapse. Int J Gynecol Pathol. 2017;36(1):31-41 https://www.ncbi.nlm.nih.gov/pubmed/27015437 (Impact Factor: 1.628)
4. Bartosch, C, Lopes, JM and Jeronimo, C. Epigenetics in endometrial carcinogenesis - part 1: DNA methylation. Epigenomics. 2017;9(5):737-55 https://www.ncbi.nlm.nih.gov/pubmed/28470096 (Impact Factor: 4.979)
5. Bartosch, C, Lopes, JM and Jeronimo, C. Epigenetics in endometrial carcinogenesis - part 2: histone modifications, chromatin remodeling and noncoding RNAs. Epigenomics. 2017;9(6):873-92 https://www.ncbi.nlm.nih.gov/pubmed/28523964 (Impact Factor: 4.979)
6. Bartosch, C, Pires, M, Jeronimo, C and Lopes, JM. The role of pathology in the management of patients with endometrial carcinoma. Future Oncol. 2017;13(11):1003-20 https://www.ncbi.nlm.nih.gov/pubmed/28481146 (Impact Factor: 2.369)
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10. Carvalho, S, Gueiral, N, Nogueira, E, Henrique, R, Oliveira, L and Tuchin, VV (2017). Comparative study of the optical properties of colon mucosa and colon precancerous polyps between 400 and 1000 nm. In Dynamics and Fluctuations in Biomedical Photonics XIV (International Society for Optics and Photonics), pp. 100631L https://www.spiedigitallibrary.org/conference-proceedings-of-spie/10063/100631L/Comparative-study-of-the-optical-properties-of-colon-mucosa-and/10.1117/12.2253023.short?SSO=1 (Impact Factor: NA)
11. Carvalho, S, Gueiral, N, Nogueira, E, Henrique, R, Oliveira, L and Tuchin, VV. Glucose diffusion in colorectal mucosa-a comparative study between normal and cancer tissues. Journal of biomedical optics. 2017;22(9):91506 https://www.ncbi.nlm.nih.gov/pubmed/28241323 (Impact Factor: 2.367)

12. Costa, AL, Lobo, J, Jeronimo, C and Henrique, R. The epigenetics of testicular germ cell tumors: looking for novel disease biomarkers. Epigenomics. 2017;9(2):155-69
https://www.ncbi.nlm.nih.gov/pubmed/28097877 (Impact Factor: 4.979)
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14. Faria, J, Barbosa, J, Leal, S, Afonso, LP, Lobo, J, Moreira, R, Queiros, O, Carvalho, F and Dinis-Oliveira, RJ. Effective analgesic doses of tramadol or tapentadol induce brain, lung and heart toxicity in Wistar rats. Toxicology. 2017;385:38-47
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15. Ferreira, AI, Borges, S, Sousa, A, Ribeiro, C, Mesquita, A, Martins, PC, Peyroteo, M, Coimbra, N, Leal, C, Reis, P and Sousa, JA. Radial scar of the breast: Is it possible to avoid surgery? European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(7):1265-72
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17. Ferreira, MJ, Pires-Luis, AS, Vieira-Coimbra, M, Costa-Pinheiro, P, Antunes, L, Dias, PC, Lobo, F, Oliveira, J, Goncalves, CS, Costa, BM, Henrique, R and Jeronimo, C. SETDB2 and RIOX2 are differentially expressed among renal cell tumor subtypes, associating with prognosis and metastization. Epigenetics. 2017;12(12):1057-64
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24. Lobo, J, Henrique, R, Monteiro, P and Lobo, C. ALK-negative anaplastic large cell lymphoma with urinary bladder involvement diagnosed in urine cytology: A case report and literature review. Diagn Cytopathol. 2017;45(4):354-8
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26. Lobo, J, Pinto, C, Freitas, M, Pinheiro, M, Vizcaino, R, Oliva, E, Teixeira, MR, Jeronimo, C and Bartosch, C. Ovarian metastasis from uveal melanoma with MLH1/PMS2 protein loss in a patient with germline MLH1 mutated Lynch syndrome: consequence or coincidence? Virchows Arch. 2017;470(3):347-52
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29. Monteiro, FL, Vitorino, R, Wang, J, Cardoso, H, Laranjeira, H, Simoes, J, Caldas, M, Henrique, R, Amado, F, Williams, C, Jeronimo, C and Helguero, LA. The histone H2A isoform Hist2h2ac is a novel regulator of proliferation and epithelial-mesenchymal transition in mammary epithelial and in breast cancer cells. Cancer letters. 2017;396:42-52 https://www.ncbi.nlm.nih.gov/pubmed/28288875 (Impact Factor: 6.491)

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32. Pires-Luis, AS, Costa-Pinheiro, P, Ferreira, MJ, Antunes, L, Lobo, F, Oliveira, J, Henrique, R and Jeronimo, C. Identification of clear cell renal cell carcinoma and oncocytoma using a three-gene promoter methylation panel. J Transl Med. 2017;15(1):149 https://www.ncbi.nlm.nih.gov/pubmed/28662726 (Impact Factor: 4.197)

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34. Ramalho-Carvalho, J, Graca, I, Gomez, A, Oliveira, J, Henrique, R, Esteller, M and Jeronimo, C. Downregulation of miR-130b~301b cluster is mediated by aberrant promoter methylation and impairs cellular senescence in prostate cancer. Journal of hematology & oncology. 2017;10(1):43 https://www.ncbi.nlm.nih.gov/pubmed/28166834 (Impact Factor: 7.333)

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37. Santos-Lopes, S, Lobo, J, Henrique, R and Oliveira, J. Epididymal metastasis from prostate adenocarcinoma: An unusual and challenging diagnosis suspected in gallium-68 prostate-specific membrane antigen-positron emission tomography/computed tomography and histologically confirmed. Urology annals. 2017;9(1):89-91 https://www.ncbi.nlm.nih.gov/pubmed/28216940 (Impact Factor: NA)

38. Torres-Ferreira, J, Ramalho-Carvalho, J, Gomez, A, Menezes, FD, Freitas, R, Oliveira, J, Antunes, L, Bento, MJ, Esteller, M, Henrique, R and Jeronimo, C. MiR-193b promoter methylation accurately detects prostate cancer in urine sediments and miR-34b/c or miR-129-2 promoter methylation define subsets of clinically aggressive tumors. Mol Cancer. 2017;16(1):26 https://www.ncbi.nlm.nih.gov/pubmed/28143614 (Impact Factor: 7.776)

39. van der Putten, LJ, van de Vijver, K, Bartosch, C, Davidson, B, Gatius, S, Matias-Guiu, X, McCluggage, WG, Toledo, G, van der Wurff, AA, Pijnenborg, JM, Massuger, LF and Bulten, J. Reproducibility of measurement of myometrial invasion in endometrial carcinoma. Virchows Arch. 2017;470(1):63-8 https://www.ncbi.nlm.nih.gov/pubmed/27787595 (Impact Factor: 2.936)

TEAM MEMBERS

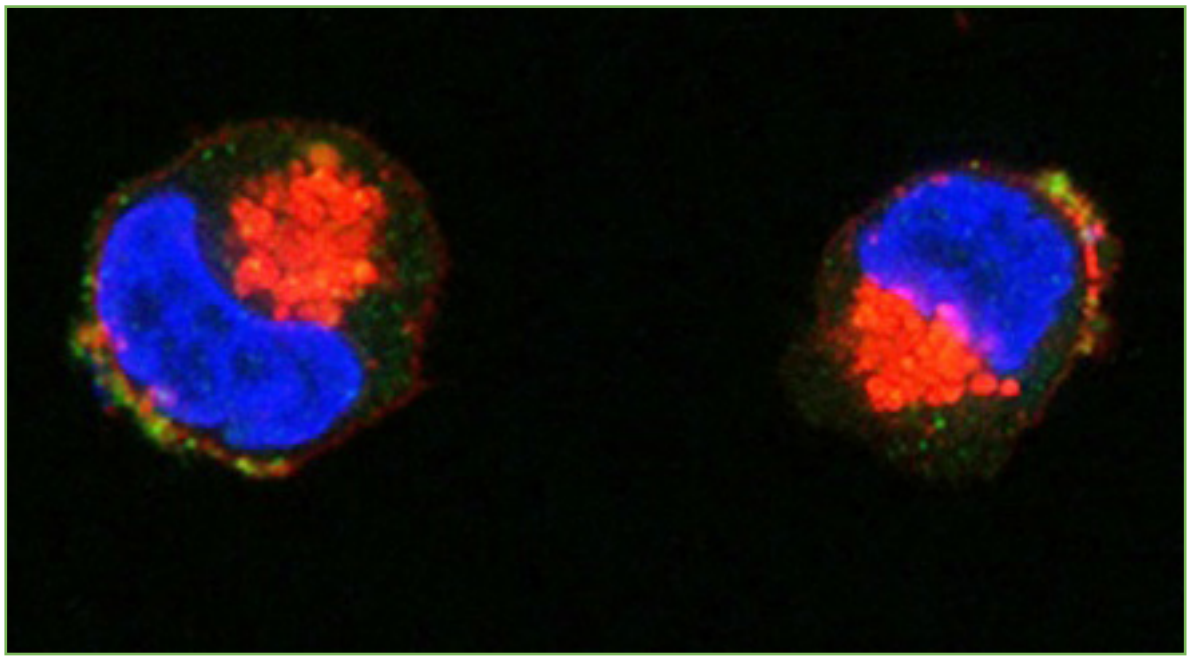
Name	Academic degree	Professional situation	Category/Position	Time %
Ana Catarina Lameirinhas	BSc	MSc Student	MSc Student	100
Ana Catarina Macedo Silva	BSc	MSc Student	MSc Student	100
Ana Filipa Quintela Vieira	PhD	Employed	Adjunct Prof. ESTSP	20
Ana Laura da Silva Costa	MSc	Not Employed	Research Trainee	100
Ana Luísa Peixoto da Costa e Cunha	MSc	Employed	Junior pathologist	10
Ana Luisa Pereira Pinto	BSc	MSc Student	MSc Student	100
Ana Paula Marques Silva Lopes Ambrosio	BSc	Employed	Lab Technician	30
Ana Sílvia Pires Luís	PhD	Employed	Resident in Pathology	20
Ana Teresa Pinto Teixeira Martins	MSc	Employed	Lab Technician	20
Ângela Isabel Marques Magalhães	MSc	Not Employed	Research Trainee	100
Ângelo Adroaldo do Amaral de Jesus Rodrigues	MSc	Employed	Junior pathologist	20
Carla Maria Magno Bartosch	PhD	Employed	Junior pathologist	20
Carmen De Lurdes Fonseca Jerónimo	Aggregation	Employed	Assistant Researcher; Group coordintor	100
Catarina Filipa Amorim Meireles	MSc	Employed	Resident in Pathology	20
Daniela Cristina Barros Silva	MSc	BI Fellowship CI-IPOP-33-2015	Research Trainee	100
Davide Gigliano	MSc	Employed	Resident in Pathology	20
Diana Leitão Montezuma P. Felizardo	MSc	Employed	Resident in Pathology	10
Fernanda Maria Ferreira da Silva	BSc	Employed	Lab Technician	10
Francisco Duarte Ferreira Menezes	MSc	Employed	Junior pathologist	10
Helena Sofia Casanova Estevão Pereira	BSc	MSc Student	MSc Student	100
Isa Cristiana Silva Carneiro	MSc	Employed	Lab Technician	20
Joana Vanessa P. Matos Loureiro	MSc	Employed	Junior pathologist	10
João Pedro da Silva Machado Lobo	MSc	FCT/SFRH/BD /132751/2017	PhD Student; Resident in Pathology	100
Jorge Silvério Torres Ferreira	MSc	Employed	Lab Technician	10
Margarida Maria Cardoso da Costa Barreto Caldas	MSc	Employed	Resident in Pathology	10
Maria Inês Pinho dos Santos Graça	PhD	MSc Student	MD Student	20
Maria José da Costa Pinho Silveira	MSc	Employed	PhD student	100
Maria Rodrigues Amorim	MSc	Not Employed	Research Trainee	100
Mariana Cantante Cordeiro da Costa Ferreira	BSc	Employed	Lab Technician	10

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Mário Filipe Teixeira de Fontes e Sousa	MSc	Employed	Resident in Oncology; PhD student	30
Mónica Alexandra Domingos Farinha	MSc	Employed	Resident in Pathology	10
Nuno David Monteiro Coimbra	MSc	Employed	Junior pathologist; PhD student	30
Paula Cristina Magalhães de Sousa Monteiro	BSc	Employed	Senior Pathologist	20
Paula Cristina Monteiro Dias	BSc	Employed	Lab Technician	20
Renata Heloísa de Oliveira Lage Vieira	BSc	Employed	Lab Technician	10
Rita Manuela Marques de Castro Guimarães	BSc	Employed	Lab Technician; MSc Student	10
Rui Manuel Ferreira Henrique	Aggregation	Employed	Senior Pathologist; Senior Researcher	30
Sandra Isabel Pinto Nunes	BSc	Employed	MSc Student	100
Sara Lopes Petronilho	MSc	Employed	Resident in Pathology	20
Sara Raquel Monteiro dos Reis	MSc	FCT Fellowship SFRH/BD/112673/2015	PhD student	100
Sofia Margarida de Castro Paupério e Silva Paulino	MSc	Employed	Lab Technician	20
Sofia Raquel Fernandes Salta	MSc	Fellowship P2020 ESTIMA	PhD student	100
Sónia Isabel Dias de Carvalho	MSc	Employed	Resident in Pathology	20
Vera Inês Salvado Constâncio	BSc	MSc Student	MSc Student	100
Vera Mónica Miranda-Gonçalves	PhD	Fellowship P2020 ESTIMA	Postdoc	100
Verónica Martins Ferreira	BSc	Employed	Lab Technician	10

CANCER DRUG RESISTANCE

GROUP LEADER: **Maria Helena Vasconcelos**



AIM OF THE GROUP

Drug resistance is a major obstacle to the successful treatment of cancer. Moreover, some tumors are multidrug resistant, presenting resistance to several drugs having different molecular targets and chemical structures. The overall objectives/research lines of our translational research are to:

i) Identify and validate novel molecular targets to overcome MDR in cancer;

ii) Identify at a pre-clinical level novel therapeutic approaches to overcome the MDR phenotype of tumour cells, particularly of cancer stem cells;

iii) Identify means to diagnose MDR and minimal residual disease in haematological tumours and support clinical decisions.

MAJOR ACHIEVEMENTS IN 2017

We clarified for the first time the complex network of metabolic alterations associated with multidrug resistance in cancer cells. In addition, we showed innovative evidence that extracellular vesicles released by those cells may cause a metabolic shift in recipient drug-sensitive cells, towards the one found in multidrug resistant cells.

We identified a novel curcumin derivative, which inhibits P-glycoprotein, arrests cell cycle and induces apoptosis in multidrug resistant cells.

We collaborated in a study, which showed that suppression of spindly enhances cell death of cancer cells treated with low doses of paclitaxel.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Lopes-Rodrigues, V, Di Luca, A, Mleczko, J, Meleady, P, Henry, M, Pesic, M, Cabrera, D, van Liempd, S, Lima, RT, O'Connor, R, Falcon-Perez, JM and Vasconcelos, MH. Identification of the metabolic alterations associated with the multidrug resistant phenotype in cancer and their intercellular transfer mediated by extracellular vesicles. Scientific reports. 2017;7:44541
   https://www.ncbi.nlm.nih.gov/pubmed/28303926 (Impact Factor: 4.122)
2. Silva, PM, Ribeiro, N, Lima, RT, Andrade, C, Diogo, V, Teixeira, J, Florindo, C, Tavares, A, Vasconcelos, MH and Bousbaa, H. Suppression of spindly delays mitotic exit and exacerbates cell death response of cancer cells treated with low doses of paclitaxel. Cancer letters. 2017;394:33-42
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   http://www.sciencedirect.com/science/article/pii/S0924224417300699 (Impact Factor: 6.609)
5. Vasconcelos, MH. Special Issue: New Approaches to Counteract Drug Resistance in Cancer. Molecules. 2016;22(1)
   https://www.ncbi.nlm.nih.gov/pubmed/28025535 (Impact Factor: 3.098)
6. Santos, FC, Fernandes, AS, Antunes, CAC, Moreira, FP, Videira, A, Marinho, HS and de Almeida, RFM. Reorganization of plasma membrane lipid domains during conidial germination. Biochimica et biophysica acta. 2017;1862(2):156-66
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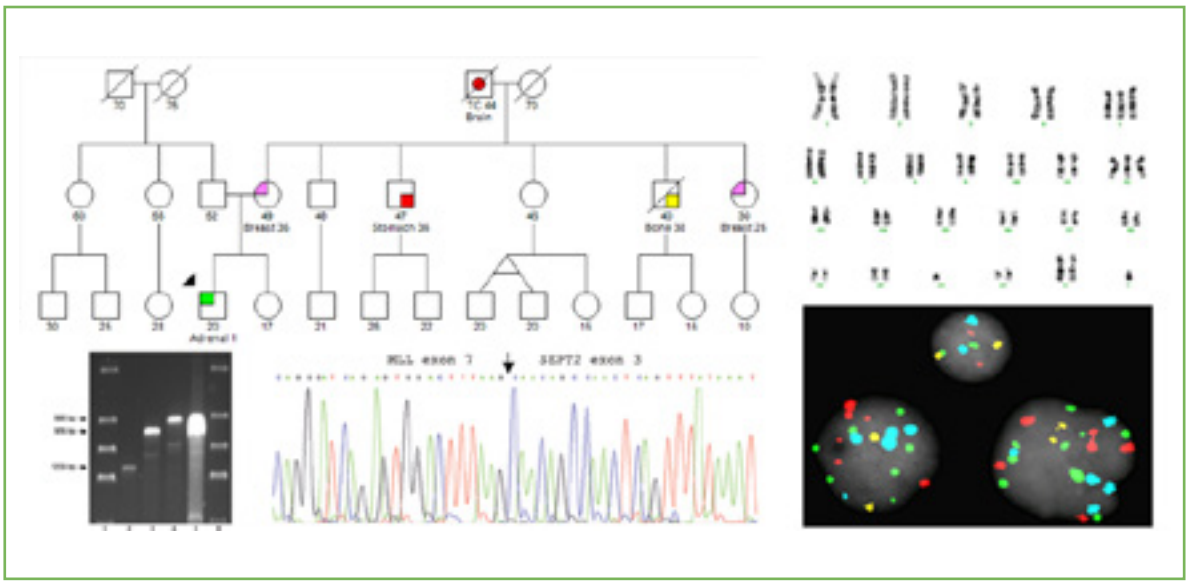
   https://www.ncbi.nlm.nih.gov/pubmed/28983298 (Impact Factor: 4.019)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Arnaldo António de Moura Silvestre Videira	Aggregation	Academia	Full Professor	50
Cristina Pinto Ribeiro Xavier	PhD	Fellowship	Post-Doc Researcher	100
Daniela Filipa Rodrigues Figueiredo	BSc	Student	MSc student	100
Déborah Carolina Batista Lopes da Cunha Matias	MSc	External	Visiting Researcher	50
Diana Duarte de Sousa	MSc	Student	PhD student	100
Hugo Lima Pereira Seca Teixeira	PhD	Researcher	Others	10
Hugo Ronaldo Freitas Caires	PhD	Fellowship	Post-Doc Researcher	100
Joana Maria Abreu Carvalho Pereira	MSc	Student	PhD student	100
José Eduardo Torres de Eckenroth Guimarães	MD, PhD	Academia	Full Professor	30
Manuel Areias Sobrinho Simões	MD, PhD	Academia	Others	30
Maria Helena da Silva de Vasconcelos Meehan	PhD	Academia	Assistant Professor	50
Maria Inês de Castro Silva	BSc	Student	MSc student	100
Mariana Ribeiro Natalino	BSc	External	Visiting Researcher	50
Marilene Sofia Rodrigues Estanqueiro	MSc	Student	PhD student	50
Ricardo Jorge Moreira Lopes Fernandes	MSc	External	Research Trainee	15
Rui Filipe Cordeiro Bergantim	MD	Student	PhD student	25
Sara Cristina Sequeira Alves	PhD	Fellowship	Post-Doc Researcher	100
Tamara Fernández Marcelo	PhD	Employed	Assistant Researcher	100

CANCER GENETICS

GROUP LEADER: **Manuel R. Teixeira**



AIM OF THE GROUP

The general objectives of the Cancer Genetics Group are to characterize the pattern of acquired genetic alterations that presumably give rise to cancer, as well as to understand the mechanisms of tumor progression and therapy response. In addition, we want to characterize the inherited mutations associated with cancer predisposition, as well as the pattern of somatic genetic changes that occur in hereditary cancer syndromes. Several biologically and clinically relevant tumor models are studied, as they can provide transversal input. To make possible tailor-made therapy specifically directed towards the altered metabolism of tumor cells, exact knowledge about the inherited and acquired genomic abnormalities of individual patients, not just about diagnostic categories, is becoming a decisive factor in the selection of the optimal therapy.

One major line of research for the next years aims to identify and characterize genetic causes predisposing to inherited prostate cancer (PCa). We have completed the recruitment of a series of 462 families with early-onset or familial PCa and performed whole exome sequence for 96 PCa patients from 45 of these families (discovery series). This project is likely to result in the identification of at least part of the missing heritability associated with highly penetrant mutations that is expected to exist in up to 10% of the PCa cases, especially those with early onset and heavy family history of the disease. Besides providing the possibility for a molecular diagnosis of inherited predisposition for these families, finding the genes will allow pre-symptomatic testing of relatives at risk. This will enable offering targeted screening to high-risk carriers, since it is likely that this will result in increased positive predictive value for biopsy as compared to population-based studies. Pre-symptomatic testing for high-risk genes will also avoid unspecific PCa screening in non-carriers of a known high-risk family mutation, thereby avoiding the risk of overdiagnosis and overtreatment in men that have the population risk despite belonging to a high-risk family. The identification of germline mutations in families with predisposition to other cancers are also secondary objectives, using next generation sequencing with gene panels or whole exome sequencing.

The second major line of research for the next years involves using circulating cell-free tumor DNA (ctDNA) to perform molecular diagnosis, predictive testing for targeted therapy, and cancer screening. In theory, somatic genetic changes present in cancer cells can be used as markers for early cancer detection, as well as during follow up to evaluate therapy response. The detection of mutations in ctDNA has emerged has a noninvasive strategy to assess primary tumors as well as eventual secondary lesions. This strategy has already been implemented in our group for monitoring the response and the mechanisms of resistance to targeted therapy and will be tested also in high-risk carriers in the context of families with hereditary breast/ovarian cancer and Lynch syndrome.

MAJOR ACHIEVEMENTS IN 2017

Validation of a next-generation sequencing pipeline for the molecular diagnosis of multiple inherited cancer predisposing syndromes

We established a next-generation sequencing analysis pipeline for the molecular diagnosis of multiple inherited cancer predisposing syndromes using the commercially available target sequencing panel TruSight Cancer. To establish the analysis pipeline, we included 22 control samples with deleterious mutations covering all genes currently analyzed at our institution by standard Sanger sequencing. We tested the pipeline using 51 samples from patients with a clinical diagnosis of neurofibromatosis type 1 (NF1), 10 of which without previous molecular characterization of the causative NF1 mutations. We propose a thoroughly validated analysis pipeline that combines Isaac Enrichment, Burrows-Wheeler Aligner Enrichment, and NextGENe for the alignment and variant calling, and GeneticistAssistant for variant annotation and prioritization. This pipeline allowed the identification of disease-causing mutations in all 73 patients, including a large duplication of 37 bp in NF1. We show that high sensitivity and specificity can be achieved by using multiple bioinformatic tools for alignment and variant calling and careful variant filtering, having in mind the clinical question (J Mol Diagn 2017, 19:502-513).

POLE somatic mutations in advanced colorectal cancer

To evaluate the role of POLE mutations in colorectal carcinogenesis, namely in advanced CRC, we searched for somatic mutations by Sanger sequencing in tumor DNA samples from 307 cases. Microsatellite instability and mutation analyses of a panel of oncogenes were performed in the tumors harboring POLE mutations. Three heterozygous mutations were found in two tumors, the c.857C>G, p.Pro286Arg, the c.901G>A, p.Asp301Asn, and the c.1376C>T, p.Ser459Phe. Of the POLE-mutated CRCs, one tumor was microsatellite-stable and the other had low microsatellite instability, whereas KRAS and PIK3CA mutations were found in one tumor each. We conclude that POLE somatic mutations exist but are rare in advanced CRC, with further larger studies being necessary to evaluate its biological and clinical implications (Cancer Med 2017, 6:2966-2971).

Performance of Lynch syndrome predictive models in quantifying the likelihood of germline mutations in patients with abnormal MLH1 immunoexpression

We evaluated if Lynch Syndrome predictive models have a role to improve the molecular testing algorithm in this specific setting by studying 38 individuals referred for molecular testing and who were subsequently shown to have loss of MLH1 immunoexpression in their tumors. Of the 38 individuals, 18.4 % had a pathogenic MLH1 germline mutation. MMRpro performed better for the purpose of this study, presenting a AUC of 0.83 (95 % CI 0.67-0.9; $P < 0.001$). Considering a threshold of 5 %, MMRpro would eliminate unnecessary germline mutation analysis in a significant proportion of cases while keeping very high sensitivity. We conclude that MMRpro is useful to correctly predict who should be screened for a germline MLH1 gene mutation and propose an algorithm to improve the cost-effectiveness of LS diagnosis (Fam Cancer 2017, 16:73-81).

Germline mutations in PALB2, BRCA1, and RAD51C, which regulate DNA recombination repair, in patients with gastric cancer

To identify genetic variants that affect risk for gastric cancer, we collected blood samples from 28 patients with hereditary diffuse gastric cancer (HDGC) not associated with mutations in CDH1 and performed whole-exome sequence analysis in a collaboration with UC Davis. We then analyzed sequences of candidate genes in 333 independent HDGC and non-HDGC cases. We identified 11 cases with mutations in PALB2, BRCA1, or RAD51C genes, which regulate homologous DNA recombination. We found these mutations in 2 of 31 patients with HDGC (6.5%) and 9 of 331 patients with sporadic gastric cancer (2.8%). Most of these mutations had been previously associated with other types of tumors and partially co-segregated with gastric cancer in our study. Tumors that developed in patients with these mutations had a mutation signature associated with somatic homologous recombination deficiency. Our findings indicate that defects in homologous recombination increase risk for gastric cancer (Gastroenterology 2017, 152:983-986 e986).

Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer

In a collaboration within the CIMBA consortium, we conducted a GWAS using 21,468 ER-negative cases and 100,594 controls combined with 18,908 BRCA1 mutation carriers (9,414 with breast cancer), all of European origin. We identified independent associations at $P < 5 \times 10\text{-}8$ with ten variants at nine new loci. At $P < 0.05$, we replicated associations with 10 of 11 variants previously reported in ER-negative disease or BRCA1 mutation carrier GWAS and observed consistent associations with ER-negative disease for 105 susceptibility variants identified by other studies. These 125 variants explain approximately 16% of the familial risk of this breast cancer subtype. There was high genetic correlation (0.72) between risk of ER-negative breast cancer and breast cancer risk for BRCA1 mutation carriers. These findings may lead to improved risk prediction and inform further fine-mapping and functional work to better understand the biological basis of ER-negative breast cancer (Nat Genet 2017, 49:1767-1778).

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D, Ganz, PA, Garber, J, Garcia, MJ, Garcia-Barberan, V, Gehrig, A, Collaborators, GS, Gentry-Maharaj, A, Gerdes, AM, Giles, GG, Glasspool, R, Glendon, G, Godwin, AK, Goldgar, DE, Goranova, T, Gore, M, Greene, MH, Gronwald, J, Gruber, S, Hahnen, E, Haiman, CA, Hakansson, N, Hamann, U, Hansen, TVO, Harrington, PA, Harris, HR, Hauke, J, Study, H, Hein, A, Henderson, A, Hildebrandt, MAT, Hillemanns, P, Hodgson, S, Hogdall, CK, Hogdall, E, Hogervorst, FBL, Holland, H, Hooning, MJ, Hosking, K, Huang, RY, Hulick, PJ, Hung, J, Hunter, DJ, Huntsman, DG, Huzarski, T, Imyanitov, EN, Isaacs, C, Iversen, ES, Izatt, L, Izquierdo, A, Jakubowska, A, James, P, Janavicius, R, Jernetz, M, Jensen, A, Jensen, UB, John, EM, Johnatty, S, Jones, ME, Kannisto, P, Karlan, BY, Karnezis, A, Kast, K, Investigators, KC, Kennedy, CJ, Khusnutdinova, E, Kiemeney, LA, Kiiski, JI, Kim, SW, Kjaer, SK, Kobel, M, Kopperud, RK, Kruse, TA, Kupryjanczyk, J, Kwong, A, Laitman, Y, Lambrechts, D, Larranaga, N, Larson, MC, Lazaro, C, Le, ND, Le Marchand, L, Lee, JW, Lele, SB, Leminen, A, Leroux, D, Lester, J, Lesueur, F, Levine, DA, Liang, D, Liebrich, C, Lilyquist, J, Lipworth, L, Lissowska, J, Lu, KH, Lubinnski, J, Luccarini, C, Lundvall, L, Mai, PL, Mendoza-Fandino, G, Manoukian, S, Massuger, L, May, T, Mazoyer, S, McAlpine, JN, McGuire, V, McLaughlin, JR, McNeish, I, Meijers-Heijboer, H, Meindl, A, Menon, U, Mensenkamp, AR, Merritt, MA, Milne, RL, Mitchell, G, Modugno, F, Moes-Sosnowska, J, Moffitt, M, Montagna, M, Moysich, KB, Mulligan, AM, Musinsky, J, Nathanson, KL, Nedergaard, L, Ness, RB, Neuhausen, SL, Nevanlinna, H, Niederacher, D, Nussbaum, RL, Odunsi, K, Olah, E, Olopade, OI, Olsson, H, Olswold, C, O'Malley, DM, Ong, KR, Onland-Moret, NC, group, Os, Orr, N, Orsulic, S, Osorio, A, Palli, D, Papi, L, Park-Simon, TW, Paul, J, Pearce, CL, Pedersen, IS, Peeters, PHM, Peissel, B, Peixoto, A, Pejovic, T, Pelttari, LM, Permuth, JB, Peterlongo, P, Pezzani, L, Pfeiler, G, Phillips, KA, Piedmonte, M, Pike, MC, Piskorz, AM, Poblete, SR, Pocza, T, Poole, EM, Poppe, B, Porteous, ME, Prieur, F, Prokofyeva, D, Pugh, E, Pujana, MA, Pujol, P, Radice, P, Rantala, J, Rappaport-Fuerhauser, C, Rennert, G, Rhiem, K, Rice, P, Richardson, A, Robson, M, Rodriguez, GC, Rodriguez-Antona, C, Romm, J, Rookus, MA, Rossing, MA, Rothstein, JH, Rudolph, A, Runnebaum, IB, Salvesen, HB, Sandler, DP, Schoemaker, MJ, Senter, L, Setiawan, VW, Severi, G, Sharma, P, Shelford, T, Siddiqui, N, Side, LE, Sieh, W, Singer, CF, Sobol, H, Song, H, Southey, MC, Spurdle, AB, Stadler, Z, Steinemann, D, Stoppa-Lyonnet, D, Sucheston-Campbell, LE, Sukiennicki, G, Sutphen, R, Sutter, C, Swerdlow, AJ, Szabo, CI, Szafron, L, Tan, YY, Taylor, JA, Tea, MK, Teixeira, MR, Teo, SH, Terry, KL, Thompson, PJ, Thomsen, LCV, Thull, DL, Tihomirova, L, Tinker, AV, Tischkowitz, M, Tognazzo, S, Toland, AE, Tone, A, Trabert, B, Travis, RC, Trichopoulou, A, Tung, N, Tworoger, SS, van Altena, AM, Van Den Berg, D, van der Hout, AH, van der Luijt, RB, Van Heetvelde, M, Van Nieuwenhuysen, E, van Rensburg, EJ, Vanderstichele, A, Varon-Mateeva, R, Vega, A, Edwards, DV, Vergote, I, Vierkant, RA, Vijai, J, Vratimos, A, Walker, L, Walsh, C, Wand, D, Wang-Gohrke, S, Wappenschmidt, B, Webb, PM, Weinberg, CR, Weitzel, JN, Wentzensen, N, Whittemore, AS, Wijnen, JT, Wilkens, LR, Wolk, A, Woo, M, Wu, X, Wu, AH, Yang, H, Yannoukakos, D, Ziogas, A, Zorn, KK, Narod, SA, Easton, DF, Amos, CI, Schildkraut, JM, Ramus, SJ, Ottini, L, Goodman, MT, Park, SK, Kelemen, LE, Risch, HA, Thomassen, M, Offit, K, Simard, J, Schmutzler, RK, Hazelett, D, Monteiro, AN, Couch, FJ, Berchuck, A, Chenevix-Trench, G, Goode, EL, Sellers, TA, Gayther, SA, Antoniou, AC and Pharoah, PDP. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017;49(5):680-91
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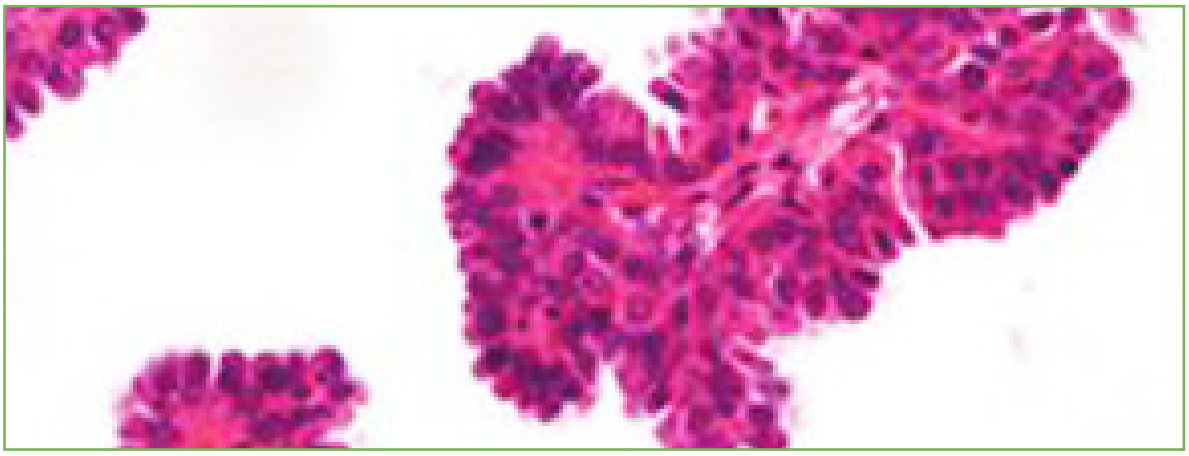
http://www.ncbi.nlm.nih.gov/pubmed/27741566 (Impact Factor: 7.360)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana de Fátima Fernandes Barbosa	BSc	Scholarship	PhD student; P2020 ESTIMA	100
Ana Luísa Pinto da Silva Lobo Peixoto de Moura	MSc	Employed IPOP	Clinical scientist	20
Andreia Filipa Moreira Aguiar Brandão	PhD	Scholarship	Postdoc; PTDC-DTPPIC-1308-2014	100
Carla Alexandra Cavaco Pinto	MSc	Employed IPOP	Clinical scientist	20
Carla Patrícia Brandão Gomes Paulo Escudeiro	MSc	Scholarship	LPCC	100
Catarina Gomes Rodrigues Santos	MSc	Employed IPOP	Clinical scientist	20
Cecília Maria Gaspar Guedes de Figueiredo e Correia	MSc	Employed IPOP	Clinical scientist	20
Daniel Ricardo Almeida dos Santos	MSc	Scholarship	LPCC	100
Isabel Maria da Silva Veiga dos Santos	MSc	Employed IPOP	Clinical scientist	20
Joana Cristina Gouveia Santos	PhD	External	Medical student	10
Joana Sofia Gonçalves Guerra	MSc	Scholarship	LPCC	100
Joana Virgínia Pinto Valejo de Magalhães Vieira	MSc	Employed IPOP	Clinical scientist	20
João Fernando Pinho Silva	BSc	Employed IPOP	Medical doctor	10
Manuel António Rodrigues Teixeira	Aggregation	Employed IPOP	Research coordinator	50
Manuela Cristina Dias Pinheiro	PhD	Scholarship	Postdoc; SFRH/BPD/113014/2015	100
Márcia Filipa Oliveira Cardoso	BSc	Scholarship	LPCC	100
Maria de Lurdes Eiras Torres	MSc	Employed IPOP	Clinical scientist	20
Maria Pedro Pessoa de Barros Pereira da Silva	MSc	Scholarship	PhD student; SFRH/ BD/132441/2017	70
Marta Ribeiro José Cardoso	MSc	Scholarship	PhD student; SFRH/BD/116557/2016	70
Nuno Manuel Botelho Gonçalves Sampaio Cerveira	PhD	Employed IPOP	Clinical scientist	30
Patrícia Maria Carvalho Rocha	MSc	Employed IPOP	Clinical scientist	20
Paula Cristina Martins dos Santos Paulo	PhD	Scholarship	Postdoc; UID/DTP/00776/2013	100
Pedro Miguel Teixeira Pinto	PhD	Scholarship	Postdoc; UID/DTP/00776/2013	100
Raquel Margarida Gomes Martins	MSc	External	Medical doctor	10
Rita Patricia Faria Dias Canário	MSc	Scholarship	PhD student; PD/BD/128001/2016	30
Rui Miguel Silva Santos	MSc	Scholarship	LPCC	100
Sofia de Melo Feiteira Maia	PhD	External	Medical doctor	10
Susana de Campos Bizarro	MSc	Employed IPOP	Clinical scientist	20
Susana Lisboa Fernandes	MSc	Employed IPOP	Clinical scientist	10

CANCER SIGNALLING & METABOLISM

GROUP LEADER: **Paula Soares**



AIM OF THE GROUP

The general subject of study of the group is the identification of molecular mechanisms of human cancer with potential applications in the diagnosis, prognosis and therapy, using as biologic models, thyroid and other neuroendocrine tumors. Besides the component of translational research, the group has basic research interests such as oncogenic signaling, survival mechanisms and mechanisms/molecules involved in mobility and invasion. Within this frame, a particular attention is paid to: a) Signalling induced by genetic alterations in tyrosine kinase receptors and signal transducing molecules involved in the MAPK and the PI3K/mTOR pathway; b) survival mechanisms of cancer cells, including telomerase reactivation and apoptosis dysregulation; c) molecular mechanisms of metabolic alterations secondary to mitochondrial DNA mutations/deletions or to mutations in nuclear genes encoding metabolic enzymes.

MAJOR ACHIEVEMENTS IN 2017

Dissecting the genetics of human cancers

We pursue the studies aiming to understand the role of telomerase promoter (TERTp) mutations in human cancer in general and in endocrine and (neuro) endocrine tumours in particular. We verified that the mutational pattern of primary cancer and of the metastastatic lesions and is different with being TERTp mutations particularly prevalent in the distant metastases (Melo M et al, 2017). We also showed that TERTp mutations are rare events in adrenocortical tumours (Pereira SS et al, 2017).

Dissecting molecular pathways in thyroid tumors

The effects of synthetic peptides antagonists of Growth Hormone-Releasing Hormone (GHRH) were evaluated in vitro and in vivo using thyroid cancer-derived cell lines and tumour samples. The biologic consequences suggest a potential anti cancer effect of these compounds (Populo H, 2017).

Irradiation and cancer

We assessed the prevalence of TERTp mutations in the Portuguese tinea capitis cohort. We find a high prevalence of these mutations in adenoma lesions of the thyroid. (Boaventura P et al, 2017).

Mitochondrial alterations and cancer

We analysed the clinico-pathological data and the protein and mRNA expression of GLUT1, GLUT4 and MCT1, MCT4 and CD147 in Papillary Renal Cell carcinoma (pRCC) from Porto and TCGA series (http://cancergenome.nih.gov/), respectively. With the exception of GLUT4, plasma membrane expression of all proteins was frequently observed in pRCCs. GLUT1 and MCT1 membrane overexpression was significantly higher in pRCC2 and significantly associated with higher pN-stage and higher Fuhrman grade. Overexpression of GLUT1, MCT1/4 and CD147, supports the metabolic reprograming in pRCCs. MCT1 expression was associated with pRCC aggressiveness, regardless of the tumour histotype (Almeida LM et al, 2016). The Etiopathogenesis of oncocytomas was reviewed (Correia M, et al, 2017)

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Bartosch, C, Lopes, JM and Jeronimo, C. Epigenetics in endometrial carcinogenesis - part 2: histone modifications, chromatin remodeling and noncoding RNAs. Epigenomics. 2017;9(6):873-92 https://www.ncbi.nlm.nih.gov/pubmed/28523964 (Impact Factor: 4.979)
2. Cappagli, V, Potes, CS, Ferreira, LB, Tavares, C, Eloy, C, Elisei, R, Sobrinho-Simoes, M, Wookey, PJ and Soares, P. Calcitonin receptor expression in medullary thyroid carcinoma. PeerJ. 2017;5:e3778 https://www.ncbi.nlm.nih.gov/pubmed/28929017 (Impact Factor: 2.118)
3. Melo, M, Gaspar da Rocha, A, Batista, R, Vinagre, J, Martins, MJ, Costa, G, Ribeiro, C, Carrilho, F, Leite, V, Lobo, C, Cameselle-Teijeiro, JM, Cavadas, B, Pereira, L, Sobrinho-Simoes, M and Soares, P. TERT, BRAF, and NRAS in Primary Thyroid Cancer and Metastatic Disease. The Journal of clinical endocrinology and metabolism. 2017;102(6):1898-907 https://www.ncbi.nlm.nih.gov/pubmed/28323937 (Impact Factor: 5.789)
4. Melo, M, Vicente, N, Ventura, M, Gaspar Da Rocha, A, Soares, P and Carrilho, F. The role of ablative treatment in differentiated thyroid cancer management. Expert Review of Endocrinology & Metabolism. 2017;12(2):109-16 https://doi.org/10.1080/17446651.2017.1289839 (Impact Factor: NA)
5. Pereira, SS, Maximo, V, Coelho, R, Batista, R, Soares, P, Guerreiro, SG, Sobrinho-Simoes, M, Monteiro, MP and Pignatelli, D. Telomerase and N-Cadherin Differential Importance in Adrenocortical Cancers and Adenomas. J Cell Biochem. 2017;118(8):2064-71 https://www.ncbi.nlm.nih.gov/pubmed/27886397 (Impact Factor: 2.959)
6. Almeida, L, Silva, R, Cavadas, B, Lima, J, Pereira, L, Soares, P, Sobrinho-Simoes, M, Lopes, JM and Maximo, V. GLUT1, MCT1/4 and CD147 overexpression supports the metabolic reprogramming in papillary renal cell carcinoma. Histol Histopathol. 2017;32(10):1029-40 https://www.ncbi.nlm.nih.gov/pubmed/28028797 (Impact Factor: 2.015)
7. Bartosch, C, Pires, M, Jeronimo, C and Lopes, JM. The role of pathology in the management of patients with endometrial carcinoma. Future Oncol. 2017;13(11):1003-20 https://www.ncbi.nlm.nih.gov/pubmed/28481146 (Impact Factor: 2.369)
8. Fraga, A, Ribeiro, R, Coelho, A, Vizcaino, JR, Coutinho, H, Lopes, JM, Principe, P, Lobato, C, Lopes, C and Medeiros, R. Genetic polymorphisms in key hypoxia-regulated downstream molecules and phenotypic correlation in prostate cancer. BMC urology. 2017;17(1):12 https://www.ncbi.nlm.nih.gov/pubmed/28143503 (Impact Factor: 1.792)
9. Rodrigues, AC, Penna, G, Rodrigues, E, Castro, P, Sobrinho-Simoes, M and Soares, P. The Genetics of Papillary Microcarcinomas of the Thyroid: Diagnostic and Prognostic Implications. Current genomics. 2017;18(3):244-54 https://www.ncbi.nlm.nih.gov/pubmed/28659720 (Impact Factor: 2.172)
10. Populo, H, Batista, R, Sampaio, C, Pardal, J, Lopes, JM and Soares, P. SDHD promoter mutations are rare events in cutaneous melanomas but SDHD protein expression is downregulated in advanced cutaneous melanoma. PloS one. 2017;12(6):e0180392 https://www.ncbi.nlm.nih.gov/pubmed/28662141 (Impact Factor: 2.766)
11. Correia, M, Pinheiro, P, Batista, R, Soares, P, Sobrinho-Simoes, M and Maximo, V. Etiopathogenesis of oncocytomas. Seminars in cancer biology. 2017;47:82-94 https://www.ncbi.nlm.nih.gov/pubmed/28687249 (Impact Factor: 10.198)
12. Bartosch, C, Lopes, JM and Jeronimo, C. Epigenetics in endometrial carcinogenesis - part 1: DNA methylation. Epigenomics. 2017;9(5):737-55 https://www.ncbi.nlm.nih.gov/pubmed/28470096 (Impact Factor: 4.979)

13. Pestana, A, Vinagre, J, Sobrinho-Simoes, M and Soares, P. TERT biology and function in cancer: beyond immortalisation. Journal of molecular endocrinology. 2017;58(2):R129-R46
https://www.ncbi.nlm.nih.gov/pubmed/28057768 (Impact Factor: 3.297)
14. Esteves, C, Maia, T, Lopes, JM and Pimenta, M. Malignant Solitary Fibrous Tumor of the Liver: AIRP Best Cases in Radiologic-Pathologic Correlation. Radiographics. 2017;37(7):2018-25
https://www.ncbi.nlm.nih.gov/pubmed/29131777 (Impact Factor: 3.249)
15. Bartosch, C, Afonso, M, Pires-Luis, AS, Galaghar, A, Guimaraes, M, Antunes, L and Lopes, JM. Distant Metastases in Uterine Leiomyosarcomas: The Wide Variety of Body Sites and Time Intervals to Metastatic Relapse. Int J Gynecol Pathol. 2017;36(1):31-41
https://www.ncbi.nlm.nih.gov/pubmed/27015437 (Impact Factor: 1.628
16. Duarte, TL, Caldas, C, Santos, AG, Silva-Gomes, S, Santos-Goncalves, A, Martins, MJ, Porto, G and Lopes, JM. Genetic disruption of NRF2 promotes the development of necroinflammation and liver fibrosis in a mouse model of HFE-hereditary hemochromatosis. Redox biology. 2017;11:157-69
https://www.ncbi.nlm.nih.gov/pubmed/27936457 (Impact Factor: 5.637
17. Cameselle-Teijeiro, JM, Rodriguez-Perez, I, Celestino, R, Eloy, C, Piso-Neira, M, Abdulkader-Nallib, I, Soares, P and Sobrinho-Simoes, M. Hobnail Variant of Papillary Thyroid Carcinoma: Clinicopathologic and Molecular Evidence of Progression to Undifferentiated Carcinoma in 2 Cases. Am J Surg Pathol. 2017;41(6):854-60
https://www.ncbi.nlm.nih.gov/pubmed/28009606 (Impact Factor: 5.878)
18. Populo, H, Nunes, B, Sampaio, C, Batista, R, Pinto, MT, Gaspar, TB, Miranda-Alves, L, Cai, RZ, Zhang, XY, Schally, AV, Sobrinho-Simoes, M and Soares, P. Inhibitory Effects of Antagonists of Growth Hormone-Releasing Hormone (GHRH) in Thyroid Cancer. Hormones & cancer. 2017;8(5-6):314-24
https://www.ncbi.nlm.nih.gov/pubmed/28924876 (Impact Factor: 2.581)
19. Boaventura, P, Batista, R, Pestana, A, Reis, M, Mendes, A, Eloy, C, Sobrinho-Simoes, M and Soares, P. TERT promoter mutations: a genetic signature of benign and malignant thyroid tumours occurring in the context of tinea capitis irradiation. Eur J Endocrinol. 2017;176(1):49-55
https://www.ncbi.nlm.nih.gov/pubmed/27760791 (Impact Factor: 4.333)
20. Pinto, ML, Rios, E, Silva, AC, Neves, SC, Caires, HR, Pinto, AT, Duraes, C, Carvalho, FA, Cardoso, AP, Santos, NC, Barrias, CC, Nascimento, DS, Pinto-do, OP, Barbosa, MA, Carneiro, F and Oliveira, MJ. Decellularized human colorectal cancer matrices polarize macrophages towards an anti-inflammatory phenotype promoting cancer cell invasion via CCL18. Biomaterials. 2017;124:211-24
https://www.ncbi.nlm.nih.gov/pubmed/28209528 (Impact Factor: 8.806)

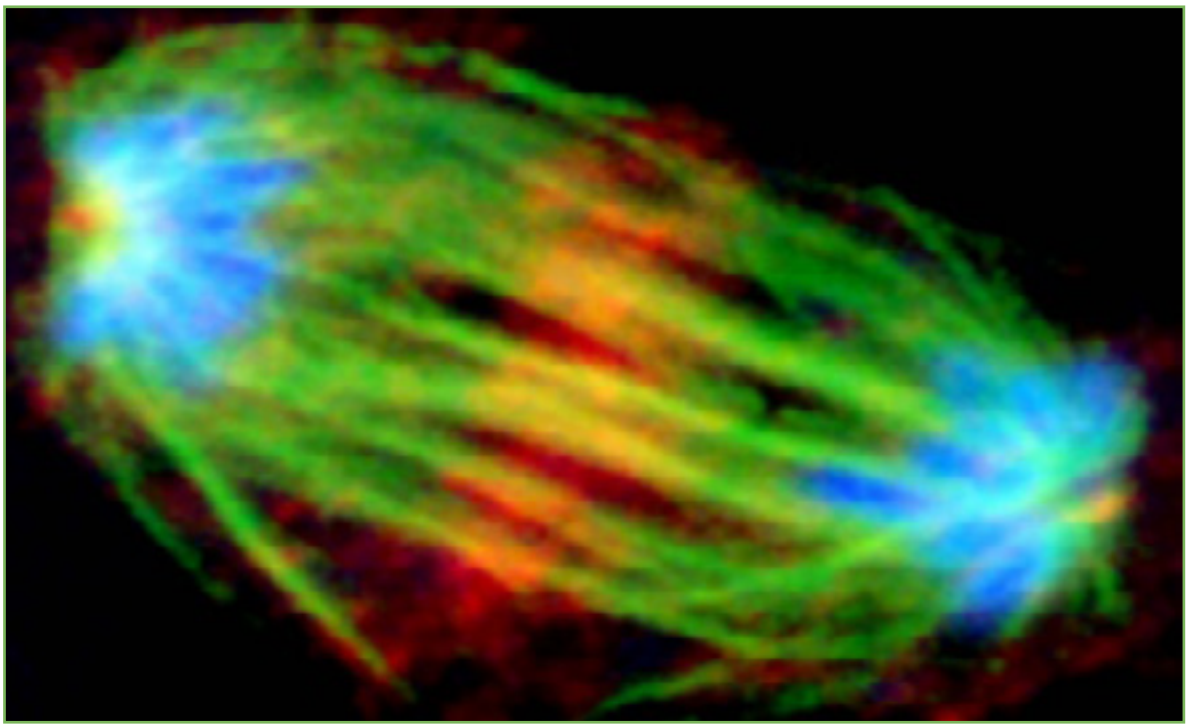
TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Adriana Maria Pinto Gaspar da Rocha	MSc	Visiting Reseacrh		50
Ana Arminda Lopes Preto	PhD	Collaborator	UM	5
Ana Catarina Marques Gomes Tavares	PhD	PhD Student	FCT	100
Ana Cristina Afonseca Pestana	MSc	PhD student	IPATIMUP	100
Ana Isabel da Rocha Sá	BSc	MSc student	ICBAS	100
Ana Paula Soares Dias Pereira	PhD	Assistant Professor	FMUP	60
Ana Rita M. Dantas de Lima	MD	PhD student	AstraZeneca	30
Ana Sofia Duarte Macedo	MSc	Research fellowship (MSc)	IPATIMUP	100
Antónia Maria Afonso Póvoa	MD	PhD student	Centro Hospitalar de V. N. Gaia	30
Beatriz Barbosa Domingues	BSc	MSc student	FCUP	70
Bruno Miguel Fernandes de Carvalho	MD	PhD student	Centro Hospitalar S. João	50
Duarte Luís Pigmatelli Dias Almeida	PhD	Associated Professor	Hospital de São João and FMUP	60
Durval Santos Marques	PhD	Visiting Reseacrh	IPATIMUP	100
Elisabete da Silva Rios	MD	Collaborator	FMUP	50
Elisabete Oliveira Teixeira	BSc	MSc student	ICBAS	100
Elsa Maria Pereira da Fonseca	PhD	Assistant Professor	FMUP	60
Helena Isabel Martins Pópulo	PhD	Assistant Research	IPATIMUP	100

Name	Academic degree	Professional situation	Category/Position	Time %
Inês de Andrade Matos Gonçalves Saraiva	BSc	MSc student	IPATIMUP	100
Joana Catarina Brás Gomes Nunes	MSc	PhD student	FCT	100
Joana Costa Aguiar de Castro Peixoto	MSc	PhD student	FCT	100
João Manuel Marques Miranda Magalhães	MSc	PhD student	Hospital de São João	30
João Pedro Rico de Oliveira Vinagre	PhD	Assistant Research	IPATIMUP	100
José Manuel Pedrosa Baptista Lopes	PhD	Assistant Professor	FMUP	60
José Miguel Lourenço Aviz Miranda Melo	PhD, MD	Collaborator	Centro Hospitalar e Univer.Coimbra	60
Liliana Pereira Santos	BSc	MSc student	ICBAS	100
Luciana Bueno Ferreira	MSc	PhD student	CNPq	100
Mafalda Maria Santos Pinto	PhD	Post-Doc Researcher	FCT	100
Manuel Alberto Coimbra Sobrinho Simões	PhD, MD, Agg	Full Professor	FMUP	60
Manuel António Costa Campos	MD	PhD student	Centro Hospitalar V. N. Gaia	50
Marcelo José Marques Correira	PhD	Post-Doc Researcher	IPATIMUP	100
Márcia Cristina Castro Sampaio	MSc	Research fellowship (BSc)	IPATIMUP	100
Maria de Fátima Machado de Magalhães	URG	Administrative Techinichan	IPATIMUP	30
Maria João Alves Ramalho	BSc	Visiting Reseacrh	FCT	20
Maria Paula Marques Boaventura	PhD	Post-Doc Researcher	IPATIMUP	100
Paula Rodrigues Pereira	MSc	PhD student	CAPES-Brasil	8
Pedro Filipe da Silva Pinheiro	BSc	PhD student	NA	100
Raquel Maria Torres Lima	PhD	Post-Doc Researcher	IPATIMUP	100
Rui Pedro Monteiro Batista	MSc	PhD student	FCT	100
Silvana Ferreira da Silva Miranda	BSc	MSc student	IPO Porto	50
Sule Canberk	MD	PhD student	Acibadem University	100
Susana Cecília de Brito Gomes Guerreiro	PhD	Post-Doc Researcher	FMUP	100
Thalita Alves	MSc	Visiting Reseacrh	Universidade de São Paulo	100
Tiago Bordeira Gaspar	MSc	PhD student	IPATIMUP	100
Valdemar de Jesus Conde Máximo	PhD	Assistant Professor	FMUP	60

CELL DIVISION & GENOMIC STABILITY

GROUP LEADER: **Claudio Sunkel**



AIM OF THE GROUP

Our group studies the mechanisms that ensure the fidelity of cell division and how failure in these mechanisms impact on genomic stability and tumorigenesis. Specifically, we aim to unravel mechanical, molecular and biochemical events underlying the segregation of chromosomes and how these are regulated to ensure the accuracy of the process.

We are studying the effects of chromosome mis-segregation in adult stem cell behavior in vivo, and how aneuploidy can lead to the development of tissue pathologies, including tumorigenic phenotypes.

We also aim to decipher how the epithelial tissue maintains its organization and cohesiveness during cell division. Given the high rate of proliferation of transformed, this knowledge is pivotal to prevent the transition of new daughter cells to a non-polarized and potentially invasive state. Moreover, we are using Drosophila to develop new in vivo models to understand how CDH1 mutants associated with hereditary diffuse gastric cancer induce tissue disorganization, cell invasion and overgrowth.

MAJOR ACHIEVEMENTS IN 2017

Extensive delay in mitosis can lead to chromosome segregation errors that often result in genomic imbalance and promote tumor development. We have unraveled a molecular mechanism that ensures timely mitotic exit. We found that following proper attachment of chromosomes to the mitotic spindle, PP1 phosphatase

inactivates the master checkpoint regulator Mps1 to ensure prompt and efficient progression through the cell cycle. This finding provides critical knowledge to understand how dividing cell avoid aneuploidy. (Moura M, Osswald M, Leça N, Barbosa J, Pereira AJ, Maiato H, Sunkel C* and Conde C*, 2017, Protein Phosphatase 1 inactivates Mps1 to ensure efficient Spindle Assembly Checkpoint silencing. eLife 6: e25366.)
Using the *Drosophila* intestine as a model, we described a unique resistance of adult stem cells to aneuploidy. Furthermore, we describe how aneuploid stem cells overproliferate and accumulate after aneuploidy induction resulting in the development of tissue dysplasia (Aneuploidy Promotes Intestinal Dysplasia in Drosophila Luis P Resende, Augusta Monteiro, Rita Bras, Tatiana Lopes, Claudio E Sunkel: bioRxiv 280768; doi: https://doi.org/10.1101/280768).

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Moura, M, Osswald, M, Leca, N, Barbosa, J, Pereira, AJ, Maiato, H, Sunkel, CE and Conde, C. Protein Phosphatase 1 inactivates Mps1 to ensure efficient Spindle Assembly Checkpoint silencing. Elife. 2017;6
   https://www.ncbi.nlm.nih.gov/pubmed/28463114 (Impact Factor: 7.616)
2. Melo, S, Figueiredo, J, Fernandes, MS, Goncalves, M, Morais-de-Sa, E, Sanches, JM and Seruca, R. Predicting the Functional Impact of CDH1 Missense Mutations in Hereditary Diffuse Gastric Cancer. Int J Mol Sci. 2017;18(12)
   https://www.ncbi.nlm.nih.gov/pubmed/29231860 (Impact Factor: 3.687)

Books & Book Chapters

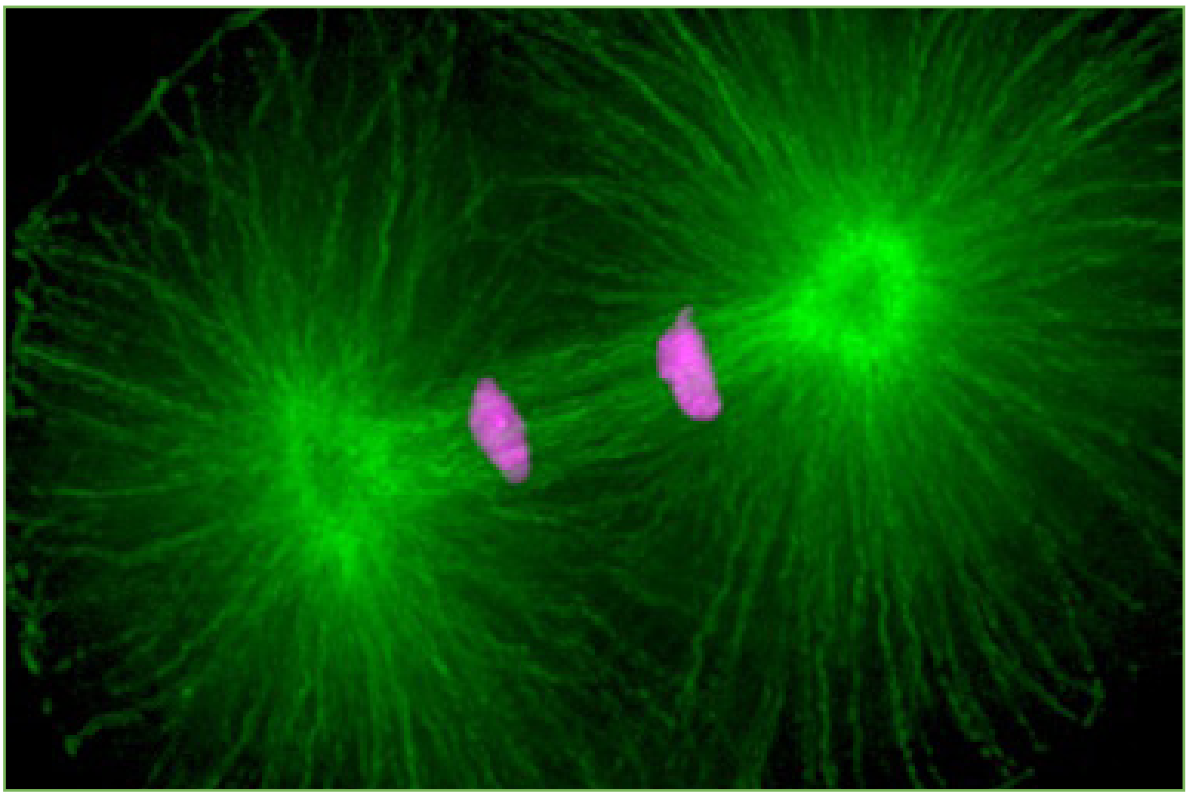
1. Thieleke-Matos, C, Osorio, DS, Carvalho, AX and Morais-de-Sa, E. Emerging Mechanisms and Roles for Asymmetric Cytokinesis. International review of cell and molecular biology. 2017;332:297-345
   https://www.ncbi.nlm.nih.gov/pubmed/28526136

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Margarida Santos	MSc	PhD student	Fellows	100
Ana Rita Brás	BSc	Msc student	Students	100
Ana Sofia Silva	MSc	PhD Student	Fellows	100
António Pombinho	PhD	Pos-Doc Research	Researchers	100
Carlos Conde	PhD	Principal Researcher	Researchers	100
Cátia Vieira	PhD	Pos-Doc Research	Researchers	100
Claudio Sunkel Cariola	PhD	Full Professor	Academia	50
Eurico Morais de Sá	PhD	Principal Researcher	Researchers	100
João Barbosa	MSc	PhD student	Students	100
Luís Pedro Resende	PhD	Pos-Doc Research	Researchers	100
Margarida Moura	MSc	PhD student	Students	100
Maria Monteiro	MSc	Research Technician	Staff	100
Mariana Osswald	MSc	PhD student	Students	100
Sofia Moreira	MSc	PhD student	Students	100

CELL DIVISION MECHANISMS

GROUP LEADER: **Reto Gassmann**



AIM OF THE GROUP

Cytoplasmic dynein 1 (dynein), a mega-dalton complex of 12 subunits, is the predominant microtubule minus end-directed motor in animals and participates in a wide range of essential cellular activities, ranging from the transport of proteins, mRNA, and vesicles to nuclear migration and cell division. Our group is interested in the regulatory mechanisms that give rise to dynein's functional diversity.

We use live-cell fluorescence microscopy, genetics, and biochemical approaches in the roundworm Caenorhabditis elegans and human cultured cells to study the roles and molecular mechanisms of co-factors that associate with dynein to modulate localization, interaction with cargo, and motor activity. We have been investigating how the 3-subunit Rod-Zw10-Zwilch complex and the adaptor protein Spindly regulate dynein function at the kinetochore, the site on chromosomes where spindle microtubules attach to drive the segregation of sister chromatids during cell division. Adaptors like Spindly have a dual role: they bring dynein together with its essential processivity factor dynactin, which is itself a multi-subunit complex, and they establish the link to diverse cargo. By studying how different adaptor families interact with dynein and dynactin, we hope to uncover general and cargo-specific mechanisms underlying the assembly and activation of the dynein-dynactin transport machinery in dividing and non-dividing cells. Mutations in dynein and its regulators are known to cause neurodegenerative disease, making a molecular understanding of dynein-driven transport medically relevant.

MAJOR ACHIEVEMENTS IN 2017

1. The molecular motor dynein is used in virtually all cellular contexts that require microtubule minus-end-directed motility. Dynein's functional diversity requires that the motor associate with co-factors and cargo-specific adaptors, but how dynein is recruited and locally activated at subcellular structures remains poorly understood on the molecular level. We obtained the most detailed view to date of how dynein is targeted to a subcellular structure: the mitotic kinetochore. Furthermore, we showed that the mechanism through which the kinetochore engages with dynein is also relevant for how cargo adaptors recruit dynein in the context of intracellular transport.
2. The intracellular position of centrosomes, which act as microtubule organizing centers, determines cell geometry and cell fate. We showed in C. elegans embryos that dynactin, an essential dynein regulator, uses its microtubule binding activity to help dynein pull on microtubules for centrosome positioning during the first mitotic division. Our work provided evidence for a novel functional link between dynactin's role in initiating transport of dynein cargo and the generation of cytoplasmic pulling forces critical for the positioning of centrosomes.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

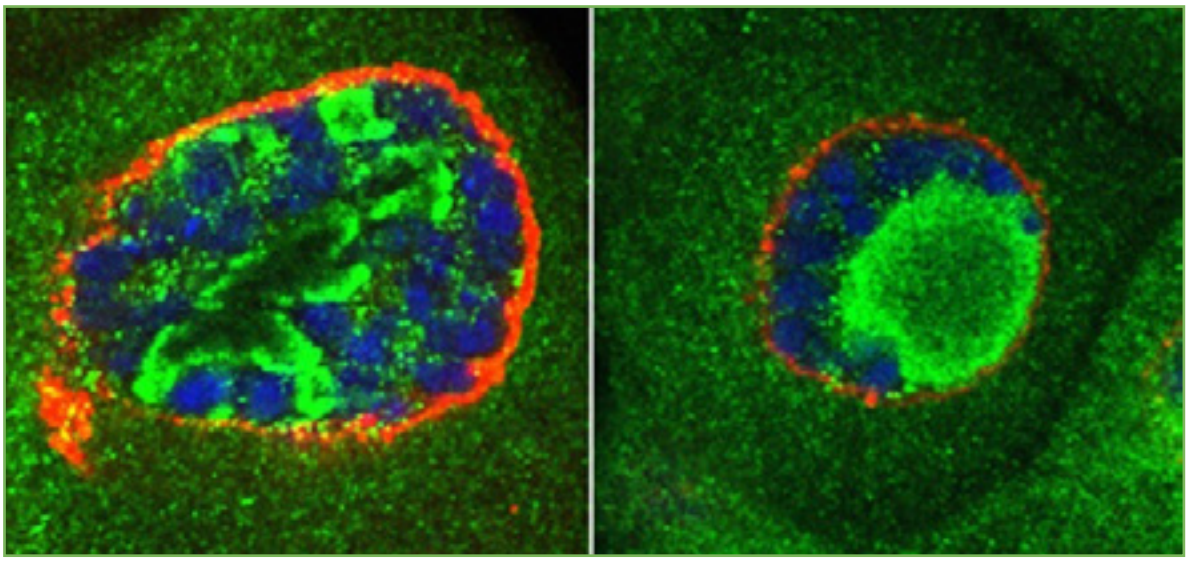
1. Gama, JB, Pereira, C, Simoes, PA, Celestino, R, Reis, RM, Barbosa, DJ, Pires, HR, Carvalho, C, Amorim, J, Carvalho, AX, Cheerambathur, DK and Gassmann, R. Molecular mechanism of dynein recruitment to kinetochores by the Rod-Zw10-Zwilch complex and Spindly. J Cell Biol. 2017;216(4):943-60
https://www.ncbi.nlm.nih.gov/pubmed/28320824 (Impact Factor: 8.784)
2. Barbosa, DJ, Duro, J, Prevo, B, Cheerambathur, DK, Carvalho, AX and Gassmann, R. Dynactin binding to tyrosinated microtubules promotes centrosome centration in C. elegans by enhancing dynein-mediated organelle transport. PLoS Genet. 2017;13(7):e1006941
https://www.ncbi.nlm.nih.gov/pubmed/28759579 (Impact Factor: 5.540)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Cátia Carvalho	BSc	Master Student	Fellowship	100
Cláudia Pereira	PhD	Post-Doc Researcher	Fellowship	100
Daniel Barbosa	PhD	Post-Doc Researcher	Fellowship	100
Helder Rocha	MSc	PhD Student	Fellowship	100
Joana Maria Fernandes	MSc	Research Assistant	Fellowship	100
José Bernardo Gama	PhD	Post-Doc Researcher	Fellowship	100
Patrícia Simões	MSc	PhD Student	Fellowship	100
Reto Gassmann	PhD	Group Leader	Contract	100
Ricardo Celestino	PhD	Post-Doc Researcher	Fellowship	100
Tânia Magalhães Silva	PhD	Post-Doc Researcher	Fellowship	100
Vanessa Teixeira	MSc	Research Assistant	Fellowship	100

CELL GROWTH & DIFFERENTIATION

GROUP LEADER: **Paulo Pereira**



AIM OF THE GROUP

Our group studies the regulation of cellular properties by transcriptional and signaling networks during organogenesis. The complex coordination of these processes makes mandatory the use of in vivo contexts for the characterization of key genes and genetic networks. For that aim, we use two genetically tractable model organisms: the fruit fly and zebrafish (team leader: Renata Freitas).

MAJOR ACHIEVEMENTS IN 2017

We have characterised a novel functional role for the oncogene Myc in Drosophila neuronal progenitors (Tavares L. PLOS Genet. 2017). We showed that decreased cellular fitness caused by reduced Drosophila Myc expression triggers non cell-autonomous activation of retinal glia proliferation and overmigration. Glia migration occurs beyond its normal limit near the boundary between differentiated photoreceptors and precursor cells, extending into the progenitor domain. This overmigration is stimulated by JNK activation (and the function of its target Mmp1), while proliferative responses are mediated by Dpp/TGFb signalling activation. This genetic model will allow the study of the crosstalk between photoreceptor progenitors and glia in normal development and during neuronal-controlled retinal gliosis.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Neto, M, Naval-Sanchez, M, Potier, D, Pereira, PS, Geerts, D, Aerts, S and Casares, F. Nuclear receptors connect progenitor transcription factors to cell cycle control. Scientific reports. 2017;7(1):4845 https://www.ncbi.nlm.nih.gov/pubmed/28687780 (Impact Factor: 4.122)
2. Tavares, L, Correia, A, Santos, MA, Relvas, JB and Pereira, PS. dMyc is required in retinal progenitors to prevent JNK-mediated retinal glial activation. PLoS Genet. 2017;13(3):e1006647 https://www.ncbi.nlm.nih.gov/pubmed/28267791 (Impact Factor: 5.540)

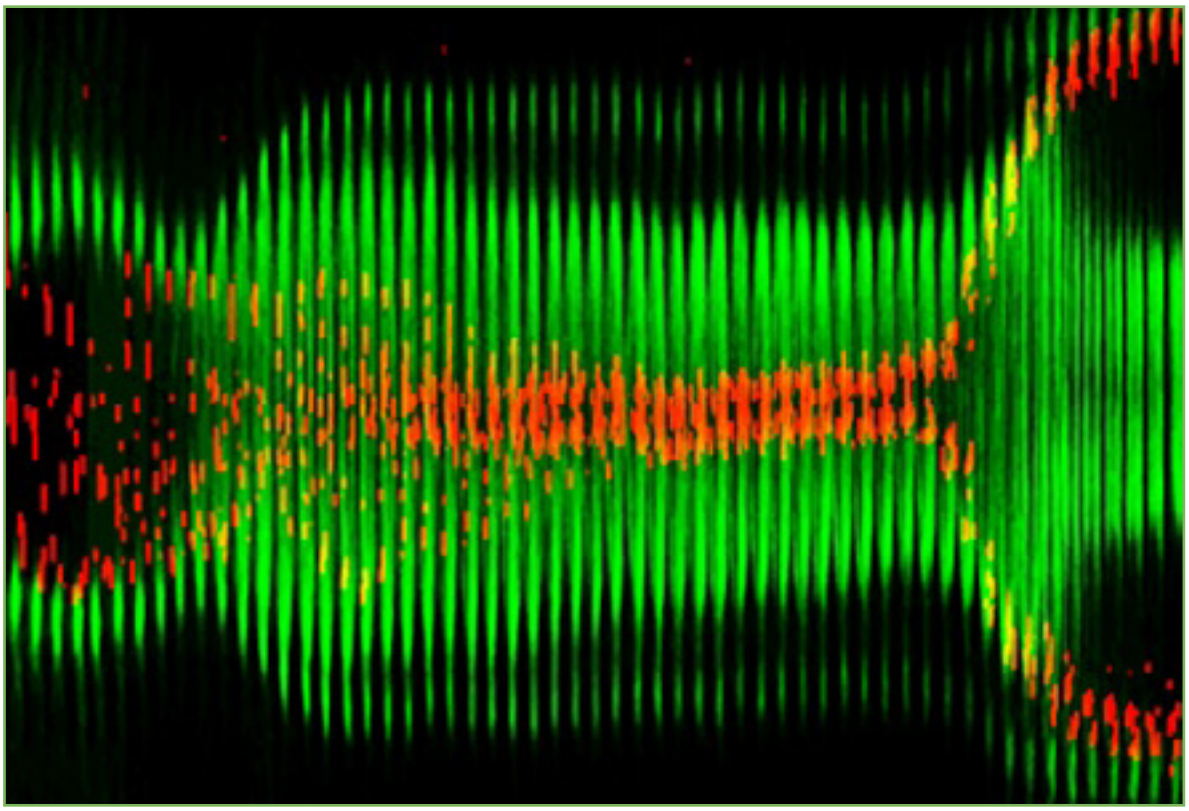
3. Martins, T, Eusebio, N, Correia, A, Marinho, J, Casares, F and Pereira, PS. TGFbeta/Activin signalling is required for ribosome biogenesis and cell growth in Drosophila salivary glands. Open biology. 2017;7(1) https://www.ncbi.nlm.nih.gov/pubmed/28123053 (Impact Factor: 3.286)
4. Paco, A and Freitas, R. Hox D genes and the fin-to-limb transition: Insights from fish studies. Genesis (New York, N.Y.: 2000). 2018;56(1) https://www.ncbi.nlm.nih.gov/pubmed/28913932 (Impact Factor: 2.667)
5. Ziermann, JM, Freitas, R and Diogo, R. Muscle development in the shark Scyliorhinus canicula: implications for the evolution of the gnathostome head and paired appendage musculature. Frontiers in zoology. 2017;14:31 https://www.ncbi.nlm.nih.gov/pubmed/28649268 (Impact Factor: 3.627)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Joanna Saab	PhD	Post-Doc Fellow	Post-Doc Researcher	100
Lígia Tavares	PhD	Post-Doc Fellow	Post-Doc Researcher	100
Mafalda Araújo	Graduate	Master Student	Master Student	100
Marta Pinho	Master	PhD Fellow	PhD Student	100
Nádia Eusébio	Master	PhD Fellow	PhD Student	100
Paulo Pereira	PhD	Principal Researcher	Group Leader	100
Renata Freitas	PhD	Assistant Researcher	Assistant Researcher	100
Simone Bessa	PhD	BIM Fellow	Post-Doc Researcher	100

CHROMOSOME INSTABILITY & DYNAMICS

GROUP LEADER: **Helder Maiato**



AIM OF THE GROUP

Mitosis is the process that ensures that dividing cells preserve the chromosome number of their progenitors, while deviation from this, a condition known as aneuploidy, represents the most common feature in human cancers. Our group is interested in the spatial and temporal control mechanisms that ensure the fidelity of chromosome segregation during mitosis. The role of the tubulin code during mitosis and the molecular regulation of the anaphase-telophase transition represent the main research lines in our laboratory.

MAJOR ACHIEVEMENTS IN 2017

We have provided a new model of chromosome congression during mitosis and contributed several conceptual pieces on the role of Actin and microtubule cross-linking in chromosome segregation, as well as on the recent identification of tubulin carboxypeptidase.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Akhmanova, A and Maiato, H. Closing the tubulin detyrosination cycle. Science. 2017;358(6369):1381-2 https://www.ncbi.nlm.nih.gov/pubmed/29242330 (Impact Factor: 41.058)

2. Maiato, H and Ferras, C. Actin divides to conquer. Science. 2017;357(6353):756-7 https://www.ncbi.nlm.nih.gov/pubmed/28839062 (Impact Factor: 41.058)
3. Figueiredo, AC and Maiato, H. Kinetochore regulation: Let there be light. Nature chemical biology. 2017;13(9):1058-9 https://www.ncbi.nlm.nih.gov/pubmed/28805799 (Impact Factor: 13.843)
4. Maiato, H and Pereira, AJ. Cell Division: NuMA Bears the Load in the Spindle. Current biology: CB. 2017;27(15):R765-R7 https://www.ncbi.nlm.nih.gov/pubmed/28787609 (Impact Factor: 9.251)
5. Maiato, H, Gomes, AM, Sousa, F and Barisic, M. Mechanisms of Chromosome Congression during Mitosis. Biology. 2017;6(1) https://www.ncbi.nlm.nih.gov/pubmed/28218637 (Impact Factor: NA)

Books & Book Chapters

1. Drpic, D and Maiato, H. Role of Nonmotor Microtubule-Associated Proteins in Mitotic Spindle Assembly. eLS2017. p. 1-9 https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470015902.a0022520

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Carvalho Figueiredo	PhD	Fellow	Post-doc Researcher	100
Ana Isabel Almeida Coelho	MSc	Fellow	PhD student	100
Ana Luísa Teixeira Ferreira	MSc	Fellow	PhD student	100
Ana Margarida Amaral Gomes	MSc	Fellow	PhD student	100
Ana Margarida Dantas Costa	MSc	Fellow	PhD student	100
António José Pereira	PhD	Fellow	Assistant Researcher	100
Ariana Jacome de Azevedo	PhD	Fellow	Post-doc researcher	100
Bernard Nunes de Almeida Orr	PhD	Researcher	Assistant Researcher	100
Carolina de Araújo Costa Ramos	PhD	Staff	Research Technician /Lab Manager	100
Danica Drpic	PhD	Fellow	Post-doc Researcher	100
Danilo da Silva Lopes	Msc	Fellow	PhD student	100
Filipe Fernandes de Sousa	MSc	External	Research Fellowship (MSc)	100
Helder José Martins Maiato	PhD	Researcher	Principal Researcher	100
Hugo Miguel Oliveira Girão	MSc	Fellow	Researcher (MSc)	100
Joaquim Jorge Gonçalves Ferreira	PhD	Academia	Assistant Professor	100
Liam Cheeseman	PhD	Researcher	Assistant Researcher	100
Marco Gabriel Novais Cruz	MSc	Fellow	PhD student	100
Maria Cristina de Madureira Ferrás da Silva	PhD	Researcher	Assistant Researcher	100
Naoyuki Okada	PhD	Fellow	Post-doc researcher	100
Vanessa Catarina Ribeiro Nunes	MSc	Fellow	PhD student	100

CLINICAL RESEARCH UNIT

GROUP LEADER: **José Dinis Silva**

AIM OF THE GROUP

IPO-Porto's Clinical Research Unit was created in 2006; its activities are supported by a professionalized team of over 50 MDs, 50 Nurses, 15 pharmacists and multiple technicians of a wide variety of areas of expertise. IPO-Porto is considered as a reference centre for Clinical Trials conducted in Portugal, in the large majority of pathologies treated in the institution. Being present at the highest level of Clinical Trials demands great discipline and dedication from all professionals.

IPO-Porto's Clinical Research Unit has a full-time dedicated team of 14 people, whose daily activity includes supporting Clinical Trials recruitment and conduct, assist in protocols compliance and support all related procedures involving the multidisciplinary professionals of the institution.

MAJOR ACHIEVEMENTS IN 2017

As a consequence of the work developed, a progressive and sustained growth on the number of Clinical Trials conducted and patients recruited has been achieved, in parallel with faster implementation timelines, with the consequent gain in competitiveness.

In 2017, more than 120 Clinical trials were ongoing, which corresponded to more than 300 patients being treated under the context of a clinical trial.

CLINICAL RESEARCH - ACTIVITY DEVELOPED IN 2017

1. Clinical studies ongoing by type, intervention and sponsor

	N° of studies		
	No Profit	Profit	Total
Experimental - drugs	0	125	125
Experimental - others	0	1	1
Experimental - total	0	126	126
Observational - drugs	52	0	52
Observational - others	2	1	3
Observational - total	54	1	55
Total	**54**	**127**	**181**

2. Number of patients on rolled and total by type of study and intervention

	N° Patients	
	2017	Total
Experimental - drugs	120	395
Observational - drugs	3	3
Observational - others	382	859
Observational - total	362	362
Total	**867**	**1 619**

3. Number of ongoing studies, number of patients on rolled and total patients by phase

	N.° Studies	N.° Patients	
		News	Total
Phase I	2	0	3
Phase II	20	7	61
Phase III	100	112	325
Phase IV	3	1	6
Total	**125**	**120**	**395**

List of active clinical trials

1. A randomized, double-blind, multicenter study of Denosumab compared with Zoledronic Acid (Zometa) in the treatment of bone disease in subjects with newly diagnosed multiple myeloma (20090482, Investigadora Principal Dra. Isabel Oliveira)
2. A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects with High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL) (20120215, Investigador Principal Dr. Armando Pinto)
3. A Randomized Phase II Study of Fulvestrant in Combination with the dual mTOR Inhibitor AZD2014 or Everolimus or Fulvestrant alone in Estrogen Receptor Positive Advanced or Metastatic Breast Cancer (009175QM MANTA, Investigadora Principal Dra. Marta Ferreira)
4. Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy versus placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma (1199.93 LUME-Meso, Investigadora Principal Dra. Marta Soares)
5. An open label trial of afatinib in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) (1200.55, Investigadora Principal Dra. Marta Soares)
6. A phase III randomized, double-blind, controlled, parallel group study of the combination of intravenous volasertib + subcutaneous low dose cytarabine (LDAC) vs. intravenous volasertib placebo + subcutaneous LDAC in patients ≥ 65 years with previously untreated AML and considered ineligible for intensive remission induction therapy (1230.14 POLO-AML-2, Investigador Principal Dr. José Mário Mariz)
7. A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer (1302.5, Investigador Principal Dr. Júlio Oliveira)
8. A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Metastatic Breast Cancer Who Have Stable Brain Metastases and Have Been Previously Treated with an Anthracycline, a Taxane, and Capecitabine (15-102-14 ATTAIN, Investigadora Principal Dra. Cláudia Vieira)
9. A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) - CHRONOS-3 (17067 CHRONOS-3, Investigador Principal Dr. Sérgio Chacim)
10. A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4 (17833 CHRONOS-4, Investigadora Principal Dra. Cláudia Moreira)
11. A randomized, double-blind, placebo-controlled, multicenter phase 3 study of Denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence (20060359 D-CARE, Investigadora Principal Dra. Rosário Couto)

12. A phase 3, randomized, double-blind trial of weekly Paclitaxel plus AMG 386 or placebo in women with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers (20090508 TRINOVA-1, Investigadora Principal Dra. Susana Sousa)
13. A Phase 1b/3 Multicenter, Trial of Talimogene Laherparepvec in Combination with Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265) (20110265 MASTERKEY-265, Investigadora Principal Dra. Paula Ferreira)
14. A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC) (212082PCR3011 LATITUDE, Investigadora Principal Dra. Joaquina Maurício)
15. A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission (2215-CL-0302 GOSSAMER, Investigadora Principal Dra. Ana Espirito Santo)
16. A multinational, randomised, double-blind, placebo-controled, phase III efficacy and safety study of ODM-201 in men with high-risk non-metastatic castration-resistant prostate cancer (3104007 ARAMIS, Investigadora Principal Dra. Joaquina Maurício)
17. A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) compared to Daratumumab in combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy (54767414MMY3007 ALCYONE, Principal Dr. Ângelo Martins)
18. Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Fulvestrant (FASLODEX) with or without PD-0332991 (PALBOCICLIB) ± Goserelin in Women with Hormone Receptor-Positive, Her2-Negative Metastatic Breast Cancer Whose Disease Progressed after Prior Endocrine Therapy (A5481023 PALOMA, Investigadora Principal Dra. Joana Bordalo e Sá)
19. A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours. (AAA-III-01 NETTER-1, Investigadora Principal Dra. Isabel Azevedo)
20. PALLAS: PALbociclib CoLlaborative Adjuvant Study: A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (ABGSG 42 PALLAS, Investigadora Principal Dra. Susana Sousa)
21. A phase 2/3, multi-center, open-label, randomized study of weekly nab®-paclitaxel in combimnation with gemcitabine or carboplatin, compared to gemcitabine/carboplatin, as first line treatment in subjects with ER, PgR, AND HER2 negative 8triple negative) metastatic breast cancer (ABI-007-MBC-001 TNACITY, Investigadora Principal Dra. Inés Pousa)
22. A Phase 3, Double-Blind, Placebo-controlled Study of Quizartinib (AC220) Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Maintenance Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First) (AC220-A-U302 QuANTUM-First, Investigador Principal Dr. Ângelo Martins)
23. A Phase 1b/2 Open-Label, Randomized Study of 2 Combinations of Isocitrate Dehydrogenase (IDH) Mutant Targeted Therapies Plus Azacitidine: Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus SC Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia Harboring an IDH1 or an IDH2 Mutation, Respectively, Who Are Not Candidates to Receive Intensive Induction Chemotherapy (AG-221-AML-005, Investigador Principal Dr. Sérgio Chacim)
24. Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma (APL-C-001-09 ADMYRE, Investigador Principal Dr. José Mário Mariz)
25. A phase 3, multicenter, randomizes, double-blind study to compare the efficacy and safety of oral azacitidine plus best supportive care versus placebo plus best supportive care in subjects with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk myelodysplastic syndromes (AZA-MDS-003, Investigadora Principal Dra. Ana Espírito Santo)
26. A phase 3, multicenter, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy (B9991001, Investigadora Principal Dra. Cátia Faustino)
27. A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of BAY 41-6551 as Adjunctive Therapy in Intubated and Mechanically-Ventilated Patients with Gram-Negative Pneumonia (13085 INHALE 2, Investigadora Principal Dra. Filomena Faria)
28. A randomised, open label, multi-centre, phase III study to investigate the efficacy of Bendamustine compared to treatment of physician's choice in the treatment of subjects with indolent Non-Hodgkin's Lymphoma (NHL) refractory to Rituximab (BDM3502 ROBIN, Investigador Principal Dr. Nelson Domingues)
29. An adaptive, comparative, randomized, parallel-group, multicenter, phase IB study of subcutaneous (SC) Rituximab versus intravenous (IV) Rituximab both in combination with chemotherapy (Fludarabine and Cyclophosphamide), in patients with previously untreated CLL (BO25341 SAWYER, Investigador Principal Dr. José Mário Mariz)

30. An open-label, multicenter extension study of trastuzumab emtansine administered as a single agent or in combination with other anti-cancer therapies in patients previously enrolled in a Genentech and /or F. Hoffmann-La Roche Ltd. - sponsored trastuzumab emtansine study (BO25430, Investigadora Principal Dra. Inés Pousa)
31. Randomized, Multicenter, Phase III, Open Label Study of Alectinib versus Crizotinib in Treatment Naïve Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer (BO28984 ALEX, Investigador Principal Dr. Júlio Oliveira)
32. A multicenter, open-label, single-arm safety study of Herceptin® SC in combination with Perjeta® and Docetaxel in treatment of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) (BO29159 MetapHer, Investigadora Principal Dra. Marta Ferreira)
33. A Phase 3, Randomized, Two-Arm, Open-Label, Multicenter, International Trial of Alisertib (MLN8237) or Investigator's Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma (C14012 LUMIERE, Investigador Principal Dr. Ângelo Martins)
34. A phase 3, randomized, double-blind, multicenter study comparing oral MLN9708 plus Lenalidomide and Dexamethasone versus placebo plus Lenalidomide and Dexamethasone in adult patients with relapsed and/or refractory multiple myeloma (C16010, Investigadora Principal Dra. Luísa Viterbo)
35. A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant (C16019, Investigador Principal Dr. Fernando Campilho)
36. A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Maintenance Therapy after Initial Therapy in Patients with Newly Diagnosed Multiple Myeloma not Treated with Stem Cell Transplantation (C16021, Investigador Principal Dr. Nelson Domingues)
37. A Phase 4, Open–label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma (C25006, Investigadora Principal Dra. Ana Espírito Santo)
38. An Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) Monotherapy in Subjects with Advanced or Metastatic Squamous Cell (Sq) Non-Small Cell Lung Cancer (NSCLC) who have received at Least Two Prior Systemic Regimens for the Treatment of Stage IIIb/IV SqNSCLC (CA209171 CheckMate 171, Investigadora Principal Dra. Marta Soares)
39. A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) for Subjects with Histologically Confirmed Stage III (unresectable) or Stage IV Melanoma Progressing Post Prior Treatment Containing an Anti-CTLA-4 Monoclonal Antibody (CA209172 CheckMate 172, Investigadora Principal Dra. Dânia Marques)
40. An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma (CheckMate 602: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 602) (CA209602 CheckMate 602, Investigador Principal Dr. José Mário Mariz)
41. A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer (CheckMate 649: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 649) (CA209649 CheckMate 649, Investigador Principal Dr. Nuno Sousa)
42. A prospective, randomized, open label two arm Phase III study to evaluate treatment free remission (TFR) rate in patients with Philadelphia-positive CML after two different durations of consolidation treatment with nilotinib 300mg BID (CAMN107AIC05 ENEST Path, Investigadora Principal Dra. Ilídia Moreira)
43. A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide (POM), Bortezomib (BTZ) and Low-Dose Dexamethasone (LD-DEX) versus Bortezomib and Low-Dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma (MM) (CC-4047-MM-007 OPTIMISMM, Investigadora Principal Dra. Luísa Viterbo)
44. A phase 3, randomized, double-blind, placebo-controlled study to compare efficacy and safety of oral azacitidine plus best supportive care versus best supportive care as maintenance therapy in vsubjects with acute myeloid leukemia in complete remission (CC-486-AML-001, Investigadora Principal Dra. Isabel Oliveira)
45. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of Lenalidomide (REVLIMID®) as maintenance therapy for patients with B-cell chronic lymphocytic leukemia following second line therapy (The CONTINUUM Trial) (CC-5013-CLL-002 CONTINUUM, Investigador Principal Dr. José Mário Mariz)
46. A phase 3, multicenter, randomized, open-label, parallel-group study of the efficacy and safety of Lenalidomide (REVLIMID®) versus Chlorambucil as first-line therapy for previously untreated elderly patients with B-cell chronic lymphocytic leukemia (The ORIGIN Trial) (CC-5013-CLL-008 ORIGIN, Investigador Principal Dr. Nelson Domingues)
47. Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide (CC-5013) plus R-CHOP Chemotherapy (R2-CHOP) versus Placebo plus R-CHOP Chemotherapy in Subjects with Previously Untreated Activated B-cell Type Diffuse Large B-cell Lymphoma (CC-5013-DLC-002 ROBUST, Investigadora Principal Dra. Isabel Oliveira)
48. A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma (CC-5013-NHL-007 AUGMENT, Investigadora Principal Dra. Cláudia Moreira)

49. Phase II trial of the addition of Lapatinib to Capecitabine versus Capecitabine alone as radio-sensitizers in KRAS wild type resectable rectal cancer (CI-IPOP.22-2012 LaRRC, Investigador Principal Dr. Nuno Sousa)
50. A randomized, double blind, placebo-controlled, multicenter, Phase III study investigating the efficacy and safety of ruxolitinib in Early Myelofibrosis patients with high molecular risk mutations (CINC424A2353 Re-THINK, Investigadora Principal Dra. Ana Espírito Santo)
51. An open-label early access phase IIIb study of trifluridine / tipiracil (S 95005/TAS-102) in patients with a pretreated metastatic colorectal cancer (CL3-95005-004, Investigadora Principal Dra. Dânia Marques)
52. A multicenter, randomized, open-label Phase 2 study evaluating the safety and efficacy of three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents (CLB-H589D2222 PANORAMA-3, Investigador Principal Dr. José Mário Mariz)
53. COMPLEEMENT-1: An open-label, multicenter, Phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease (CLEE011A2404 COMPLEEMENT-1, Investigadora Principal Dra. Ana Ferreira)
54. A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer (CLEE011E2301 MONALEESA-7, Investigadora Principal Dra. Susana Sousa)
55. A randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment (CLEE011F2301 MONALEESA-3, Investigadora Principal Dra. Ana Ferreira)
56. A randomized Phase III, open label, multicenter, two-arm study comparing MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma (CMEK162A2301 NEMO, Investigadora Principal Dra. Paula Ferreira)
57. A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma (CMEK162B2301 COLUMBUS, Investigadora Principal Dra. Paula Ferreira)
58. A phase III, double-blinded, randomized, placebo-controlled study of atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib in previously untreated BRAFV600 mutation–positive patients with unresectable locally advanced or metastatic melanoma (CO39262 TRILOGY, Investigadora Principal Dra. Paula Ferreira)
59. A phase III, randomized, double-blind, placebo-controlled, multicenter trial testing ipatasertib plus abiraterone plus prednisone/prednisolone, relative to placebo plus abiraterone plus prednisone/prednisolone in adult male patients with asymptomatic or mildly symptomatic, previously untreated, metastatic castrate-resistant prostate cancer (CO39303 IPATential 150, Investigadora Principal Dra. Cátia Faustino)
60. A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Two Prior Anti-HER2 Therapies and Require Systemic Treatment (CP-MGAH22-04 SOPHIA, Investigador Principal Dr. Miguel Abreu)
61. An open-label, phase II, single-arm study of everolimus in combination with letrozole in the treatment of postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer (CRAD001Y24135 BOLERO 4, Investigadora Principal Dra. Inés Pousa)
62. A Phase 3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Compare Efficacy and Safety between CT-P10 and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma (CT-P10 3.4, Investigador Principal Dr. José Mário Mariz)
63. An Open-Label, Comparative Trial to Evaluate the Effect of imILTin Patients with Advanced Disease or Stage IV Pancreatic Carcinoma (CTP-2015-006, Investigador Principal Dr. Belarmino Gonçalves)
64. A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (D081CC00006 OLYMPIA, Investigador Principal Dr. Miguel Abreu)
65. A Phase III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 in Combination with Tremelimumab Therapy Versus Standard of Care Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC) (D419AC00003 NEPTUNE, Investigadora Principal Dra. Marta Soares)
66. A phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 versus a standard of care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as first-line treatment in patients with Epidermal Growth Factor Receptor Mutation Positive, locally advanced or Metastatic Non-Small Cell Lung Cancer (D5160C00007 FLAURA-1, Investigadora Principal Dra. Marta Soares)

67. A Randomized, Double-blind, Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs. 14 mg QD) in Combination with Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment (E7080-G000-218, Investigadora Principal Dra. Joaquina Maurício)
68. A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of E7080 in 131I-refractory differentiated thyroid cancer (E7080-G000-303 SELECT, Investigadora Principal Dra. Isabel Azevedo)
69. A phase 3 randomized, open-label, multicenter study comparing Isatuximab (SAR650984) in Combination with pomalidomide And low-dose dexamethasone veRsus pomalidomide and low-dose dexamethasone In patients with refractory or relapsed And refractory Multiple Myeloma (EFC14335 ICARIA-MM, Investigadora Principal Dra. Cláudia Moreira)
70. A phase III trial to compare the safety and efficacy of Lapatinib plus Trastuzumab plus an aromatase inhibitor (AI) versus Trastuzumab plus an AI versus Lapatinib plus an AI as first-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received Trastuzumab and endocrine therapy in the neoadjuvant and/or adjuvant setting (EGF114299 ALTERNATIVE, Investigadora Principal Dra. Inês Pousa)
71. A Phase III, open-label, multicenter trial of avelumab (MSB0010718C) versus platinum based doublet as a first line treatment of recurrent or Stage IV PD L1+ non small cell lung cancer (EMR 100070-005 JAVELIN Lung 100, Investigadora Principal Dra. Marta Soares)
72. Apixaban for the treatment of venous thromboembolism in patients with cancer: a prospective randomized open blinded endpoint (PROBE) study - the Caravaggio study (FADOI 03.2016 CARAVAGGIO, Investigadora Principal Dra. Maria Rosales Sueiro)
73. A phase III, randomized, double-blind, placebo-controlled study of vemurafenib (RO5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence (GO27826 BRIM8, Investigadora Principal Dra. Paula Ferreira)
74. An Open-label, Extension (Rollover) Study of Vemurafenib in Patients with BRAFV600 Mutation-positive Malignancies Previously Enrolled in an Antecedent Vemurafenib Protocol (GO28399, Investigadora Principal Dra. Dânia Marques)
75. A phase II randomized, double-blind study of neoadjuvant letrozole plus GDC-0032 versus letrozole plus placebo in postmenopausal women with ER-positive/HER2-negative, early stage breast cancer (GO28888 LORELEI, Investigador Principal Dr. Júlio Oliveira)
76. A phase III, open-label, multicentre, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (GO28915 OAK, Investigadora Principal Dra. Ana Rodrigues)
77. A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Taselisib plus Fulvestrant versus Placebo plus Fulvestrant in Postmenopausal Women with Estrogen Receptor-Positive and HER2-Negative Locally Advanced or Metastatic Breast Cancer who have Disease Recurrence or Progression during or after Aromatase Inhibitor Therapy (GO29058 SANDPIPER, Investigadora Principal Dra. Susana Sousa)
78. A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy (GO29294, Investigadora Principal Dra. Joaquina Maurício)
79. A Phase III, Open-Label, Randomized Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination with Carboplatin + Paclitaxel with or without Bevacizumab compared with Carboplatin + Paclitaxel + Bevacizumab in Chemotherapy-Naïve Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer (GO29436, Investigadora Principal Dra. Isabel Azevedo)
80. A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of MPDL3280A (anti-PD-L1 Antibody) in Combination with Carboplatin + Paclitaxel or MPDL3280A in Combination with Carboplatin + Nab-Paclitaxel Versus Carboplatin + Nab-Paclitaxel in Chemotherapy Naïve Patients with Stage IV Squamous Non-Small Cell Lung Cancer (GO29437, Investigadora Principal Dra. Ana Rodrigues)
81. A phase II randomized, double-blind study of ipatasertib (GDC-0068), an inhibitor to AKT in combination with paclitaxel as neoadjuvant treatment for patients with early stage triple negative breast cancer (GO29505 FAIRLANE, Investigador Principal Dr. Júlio Oliveira)
82. A phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in PD-L1-selected patients with completely resected stage IB–IIIA non-small cell lung cancer (GO29527, Investigador Principal Dr. Júlio Oliveira)
83. A randomized, controlled, double-blind phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus CVP vs. MabThera® plus CVP, followed by GP2013 or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma. (GP13-301, Investigadora Principal Dra. Ilídia Moreira)
84. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia (GS-US-312-0115 TUGELA, Investigador Principal Dr. Ângelo Martins)
85. A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Obinutuzumab Compared to Chlorambucil in Combination with Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia (GS-US-312-0118 VICTORIA, Investigador Principal Dr. José Mário Mariz)

86. GRAVITAS-301: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft-Versus-Host Disease (INCB 39110-301 GRAVITAS-301, Investigador Principal Dr. Carlos Pinho Vaz)
87. A Phase 3 Randomized, Open-Label Study Comparing Pexa-Vec (Vaccinia GM-CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy (JX594-HEP024 PHOCUS, Investigadora Principal Dra. Maria Fragoso)
88. A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors (LOXO-TRK-15002 NAVIGATE, Investigador Principal Dr. Nuno Sousa)
89. An open-label study to investigate the tolerability, pharmacokinetics and anti-tumour effect following photodynamic therapy (PDT) with single-ascending doses of LUZ11 in patients with advanced head and neck cancer (LUZ11-CDU-001, Investigador Principal Prof. Dr. Lúcio Lara Santos)
90. Randomized, Double-Blind, Multicenter, Phase 3 Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC) (M11-089, Investigadora Principal Dra. Marta Soares)
91. A Phase III Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel with or without the PARP Inhibitor Veliparib (ABT-888) in Her-2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer (M12-914, Investigador Principal Dr. Miguel Abreu)
92. Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I) (M15-550 VENICE-I, Investigador Principal Dr. José Mário Mariz)
93. A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy (M15-656, Investigador Principal Dr. Ângelo Martins)
94. A Randomized Multicenter, Open-label, Phase 2 Study Evaluating the Efficacy and Safety of Azacitidine Subcutaneous in Combination With Durvalumab (MEDI4736) in Previously Untreated Subjects with Higher-Risk Myelodysplastic Syndromes (MDS) or in Elderly (≥ 65 years) Acute Myeloid Leukemia (AML) Subjects Not Eligible for Hematopoietic Stem Cell Transplantation (HSCT) (MEDI4736-MDS-001 FUSION, Investigadora Principal Dra. Ilídia Moreira)
95. A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (MK3475-010, Investigadora Principal Dra. Marta Soares)
96. A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer (MK3475-040, Investigador Principal Dr. José Dinis)
97. Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (MK3475-054 EORTC 1325, Investigadora Principal Dra. Paula Ferreira)
98. A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059) (MK3475-059, Investigadora Principal Dra. Manuela Machado)
99. A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (MK3475-091 PEARLS, Investigadora Principal Dra. Marta Soares)
100. A Phase III Randomized Open-label Study of Single Agent Pembrolizumab vs Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (MK3475-181 KEYNOTE-181, Investigadora Principal Dra. Paula Ferreira)
101. A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC) (MK3475-522, Investigadora Principal Dra. Marta Ferreira)
102. A Phase 3 Randomized, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Epacadostat, Pembrolizumab Monotherapy, and the EXTREME Regimen as First line Treatment for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-669/ECHO-304) (MK3475-669, Investigador Principal Dr. José Dinis)
103. A phase 3 randomized study of the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive Aspergillosis in adults (Phase 3; Protocol No. MK5592-069, Investigador Principal Dr. José Mário Mariz)
104. Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor. (ML25434 MUTAR, Investigadora Principal Dra. Marta Soares)
105. A multicenter, open-label, single-arm study of Pertuzumab in combination with Trastuzumab and a taxane in first line treatment of patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer (MO28047 PerUse, Investigadora Principal Dra. Ana Ferreira)

106. A phase III prospective, two-cohort non-randomized, multi-centre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Trastuzumab as adjuvant therapy in patients with operable HER2-positive early breast cancer [SafeHer study] (MO28048 SafeHer, Investigadora Principal Dra. Ana Ferreira)
107. Phase I study of the combination of trastuzumab emtansine (T-DM1) and capecitabine in HER2-positive metastatic breast cancer and HER2-positive locally advanced/metastatic gastric cancer patients, followed by a randomized, open-label phase II study of trastuzumab emtansine and capecitabine versus trastuzumab emtansine alone in HER2-positive metastatic breast cancer (MO28230 TRAX-HER2, Investigadora Principal Dra. Inés Pousa)
108. A multicenter, single arm study of trastuzumab emtansine (T-DM1) IN HER2-positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment (MO28231 KAMILLA, Investigadora Principal Dra. Cláudia Vieira)
109. A multicenter, open-label, single-arm, phase IIIb, international study evaluating the safety of Obinutuzumab alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory Chronic Lymphocytic Leukemia (MO28543 GREEN, Investigador Principal Dr. Sérgio Chacim)
110. A Multicentre Open-Label Single-Arm Phase II Study Evaluating the Safety and Efficacy of Bevacizumab in Combination with Carboplatin and Paclitaxel in Patients with Metastatic, Recurrent or Persistent Cervical Cancer (MO29594 CECILIA, Investigadora Principal Prof. Dra. Deolinda Pereira)
111. Randomized, Multicentre, Phase III, Open-Label Stud of Alectinib versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase-Positive Advanced Non Small Cell Lung Cancer Patients Previously Treated with Platinum-Based Chemotherapy and Crizotinib (MO29750 ALUR, Investigador Principal Dr. Júlio Oliveira)
112. A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment-naïve advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) non-small cell lung cancer who are deemed unsuitable for platinum-containing therapy" (MO29872 IPSOS, Investigador Principal Dr. Júlio Oliveira)
113. An open label, single arm, multicenter, safety study of atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract (MO29983 SAUL, Investigadora Principal: Dra. Filipa Carneiro)
114. A Phase II/III, Randomised, Multicentre Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT) – B-MIND (MOR208C204 B-MIND, Investigadora Principal: Dra. Dulcineia Pereira)
115. Randomized, double-blind, placebo-controlled phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor, in combination with Bendamustine and Rituximab (BR) in subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (PCI32765CLL3001 HELIOS, Investigadora Principal Dra. Ana Espírito Santo)
116. A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma (PCYC-1141-CA, Investigador Principal Dr. José Mário Mariz)
117. Randomised Phase II Study comparing, as first-line chemotherapy, single-agent Oral Vinorelbine administered with two different schedules in patients with Advanced Breast Cancer (PM 0259 CA 233 BO TempoBreast-1, Investigadora Principal Dra. Rosário Couto)
118. Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial) (PM1183-C-003-14 ATLANTIS, Investigadora Principal Dra. Marta Soares)
119. A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients (PR-30-5010-C BRAVO, Investigadora Principal Dra. Ana Rodrigues)
120. A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2-Directed Regimens in the Metastatic Setting (PUMA-NER-1301 NALA, Investigadora Principal Dra. Susana Sousa)
121. Double blind randomized phase III study of Lenalidomide (REVLIMID®) maintenance versus placebo in responding elderly patients with DLBCL and treated with R-CHOP in first line (REMARC, Investigador Principal Dr. José Mário Mariz)
122. A Randomized, Double Blind, Multicenter, Parallel-group, Phase III study to evaluate efficacy and safety of DCVAC/PCa versus Placebo in Men with metastatic Castration Resistant Prostate Cancer eligible for 1st line chemotherapy (SP005 VIABLE, Investigador Principal Dr. Nuno Sousa)
123. Randomized, double-blind, phase 3 study evaluating TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer refractory to standard treatments (TO-TAS-102-302, Investigadora Principal Dra. Cátia Faustino)

124. A multicenter, multinational, phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with KER2-positive, locally advanced, inflammatory, or early-stage breast cancer (WO29217 BERENICE, Investigadora Principal Dra. Claúdia Vieira)
125. A phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti–PD-L1 antibody) as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma (WO30070 IMvigor130, Investigador Principal Dr. Nuno Sousa)
126. A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy (XL184-308 METEOR, Investigador Principal Dr. Nuno Sousa)

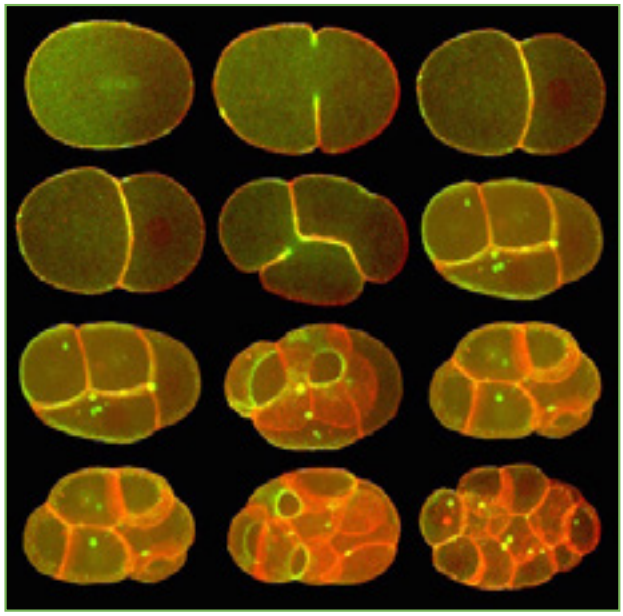
PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Avet-Loiseau, H, Bahlis, NJ, Chng, WJ, Masszi, T, Viterbo, L, Pour, L, Ganly, P, Palumbo, A, Cavo, M, Langer, C, Pluta, A, Nagler, A, Kumar, S, Ben-Yehuda, D, Rajkumar, SV, San-Miguel, J, Berg, D, Lin, J, van de Velde, H, Esseltine, DL, di Bacco, A, Moreau, P and Richardson, PG. Ixazomib significantly prolongs progression-free survival in high-risk relapsed/refractory myeloma patients. Blood. 2017;130(24):2610-8
https://www.ncbi.nlm.nih.gov/pubmed/29054911 (Impact Factor: 15.132)
2. Basset-Seguin, N, Hauschild, A, Kunstfeld, R, Grob, J, Dreno, B, Mortier, L, Ascierto, PA, Licitra, L, Dutriaux, C, Thomas, L, Meyer, N, Guillot, B, Dummer, R, Arenberger, P, Fife, K, Raimundo, A, Dika, E, Dimier, N, Fittipaldo, A, Xynos, I and Hansson, J. Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. Eur J Cancer. 2017;86:334-48
http://www.ncbi.nlm.nih.gov/pubmed/29073584 (Impact Factor: 7.191)
3. Jurczak, W, Moreira, I, Kanakasetty, GB, Munhoz, E, Echeveste, MA, Giri, P, Castro, N, Pereira, J, Akria, L, Alexeev, S, Osmanov, E, Zhu, P, Alexandrova, S, Zubel, A, Harlin, O and Amersdorffer, J. Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study. The Lancet. Haematology. 2017;4(8):e350-e61
http://www.ncbi.nlm.nih.gov/pubmed/28712941 (Impact Factor: 10.698)
4. Mateos, MV, Masszi, T, Grzasko, N, Hansson, M, Sandhu, I, Pour, L, Viterbo, L, Jackson, SR, Stoppa, AM, Gimsing, P, Hamadani, M, Borsaru, G, Berg, D, Lin, J, Di Bacco, A, van de Velde, H, Richardson, PG and Moreau, P. Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. Haematologica. 2017;102(10):1767-75
http://www.ncbi.nlm.nih.gov/pubmed/28751562 (Impact Factor: 9.09)
5. Mondelaers, V, Suciu, S, De Moerloose, B, Ferster, A, Mazingue, F, Plat, G, Yakouben, K, Uyttebroeck, A, Lutz, P, Costa, V, Sirvent, N, Plouvier, E, Munzer, M, Poiree, M, Minckes, O, Millot, F, Plantaz, D, Maes, P, Hoyoux, C, Cave, H, Rohrlich, P, Bertrand, Y, Benoit, Y, Children-s Leukemia Group of the European Organization for, R and Treatment of, C. Prolonged versus standard native E. coli asparaginase therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: final results of the EORTC-CLG randomized phase III trial 58951. Haematologica. 2017;102(10):1727-38
http://www.ncbi.nlm.nih.gov/pubmed/28751566 (Impact Factor: 9.09)
6. Rugo, HS, Tredan, O, Ro, J, Morales, SM, Campone, M, Musolino, A, Afonso, N, Ferreira, M, Park, KH, Cortes, J, Tan, AR, Blum, JL, Eaton, L, Gause, CK, Wang, Z, Im, E, Mauro, DJ, Jones, MB, Denker, A and Baselga, J. A randomized phase II trial of ridaforolimus, dalotuzumab, and exemestane compared with ridaforolimus and exemestane in patients with advanced breast cancer. Breast Cancer Res Treat. 2017;165(3):601-9
http://www.ncbi.nlm.nih.gov/pubmed/28681171 (Impact Factor: 3.605)
7. Singer, S, Jordan, S, Locati, LD, Pinto, M, Tomaszewska, IM, Araujo, C, Hammerlid, E, Vidhubala, E, Husson, O, Kiyota, N, Brannan, C, Salem, D, Gamper, EM, Arraras, JI, Ioannidis, G, Andry, G, Inhestern, J, Gregoire, V, Licitra, L, Eortc Quality of Life Group, tEH, Neck Cancer, G and the, EETF. The EORTC module for quality of life in patients with thyroid cancer: phase III. Endocrine-related cancer. 2017;24(4):197-207
http://www.ncbi.nlm.nih.gov/pubmed/28223365 (Impact Factor: 5.331)

CYTOSKELETAL DYNAMICS

GROUP LEADER: **Ana Xavier Carvalho**



AIM OF THE GROUP

Our group is interested in dissecting the fundamental mechanisms of cytokinesis, which is the process that completes mitosis by physically partitioning the contents of the mother cell into two daughter cells. We are interested in advancing the current knowledge on the acto-myosin cytoskeletal dynamics, mechanics and molecular mechanisms that control this highly temporally and spatially regulated cell process.

MAJOR ACHIEVEMENTS IN 2017

We functionally dissected the differential contributions of branched and non-branched actin filament networks during cytokinesis. We found that the actin cytoskeleton changes significantly when either the formins or the ARP2/3 complex (actin filament nucleators that give rise to non-branched or branched networks, respectively) are perturbed during cytokinesis. Our data reveled that, in contrast to the current accepted model of cytokinesis, both the ARP2/3 complex and the formin CYK-1 positively contribute to cytokinesis in C. elegans embryos. Importantly, we find that the ARP2/3 complex is required to prevent an excess of formin activity at the cell cortex, which would be detrimental for cytokinesis (unpublished).

We also determined the relevance of the myosin motor activity during cytokinesis, since previous reports have proposed its dispensability. We capitalized on the CRISPR-Cas9 technology to directly edit the C. elegans genome, and generated worms expressing motor-partially compromised or motor dead mutant myosins. Through in vivo phenotypic characterization of embryonic cytokinesis in the presence of mutant myosins, together with in vitro biochemical characterization of the molecule, we showed that motor-dead myosin does not support cytokinesis and that the actin-cross linking ability of myosin is not sufficient for embryonic cytokinesis in C. elegans, contrary to what has been suggested in other systems (unpublished).

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Vieira, N, Bessa, C, Rodrigues, AJ, Marques, P, Chan, FY, de Carvalho, AX, Correia-Neves, M and Sousa, N. Sorting nexin 3 mutation impairs development and neuronal function in Caenorhabditis elegans. Cellular and molecular life sciences : CMLS. 2018;75(11):2027-44
https://www.ncbi.nlm.nih.gov/pubmed/29196797 (Impact Factor: 6.721)
2. Barbosa, DJ, Duro, J, Prevo, B, Cheerambathur, DK, Carvalho, AX and Gassmann, R. Dynactin binding to tyrosinated microtubules promotes centrosome centration in C. elegans by enhancing dynein-mediated organelle transport. PLoS Genet. 2017;13(7):e1006941
https://www.ncbi.nlm.nih.gov/pubmed/28759579 (Impact Factor: 5.54)
3. Gama, JB, Pereira, C, Simoes, PA, Celestino, R, Reis, RM, Barbosa, DJ, Pires, HR, Carvalho, C, Amorim, J, Carvalho, AX, Cheerambathur, DK and Gassmann, R. Molecular mechanism of dynein recruitment to kinetochores by the Rod-Zw10-Zwilch complex and Spindly. J Cell Biol. 2017;216(4):943-60
https://www.ncbi.nlm.nih.gov/pubmed/28320824 (Impact Factor: 8.784)

Books, & Book Chapters

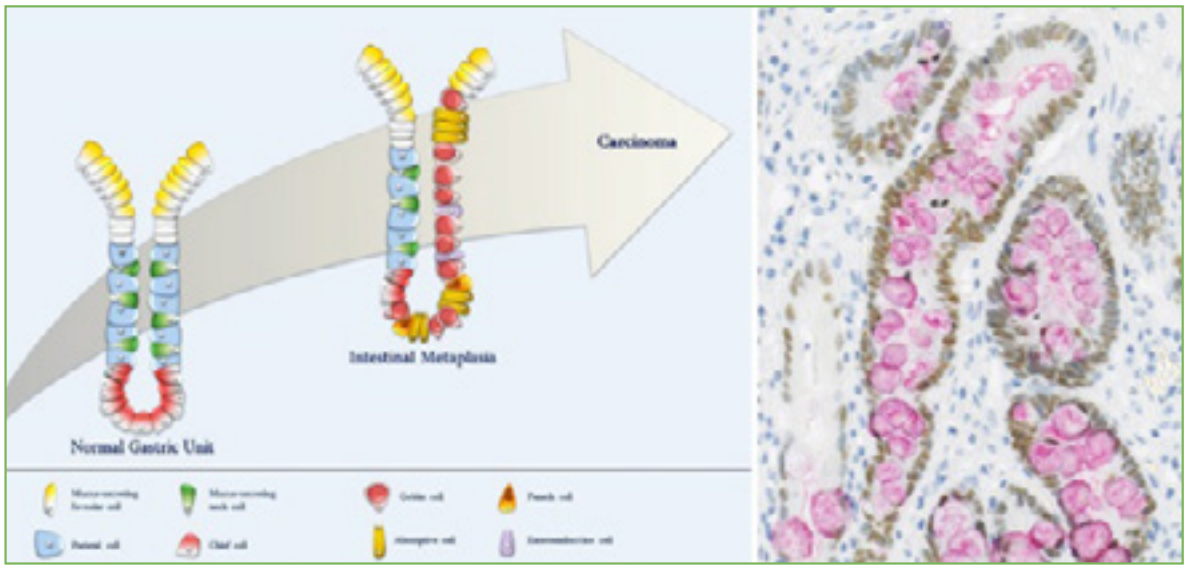
1. Thieleke-Matos, C, Osorio, DS, Carvalho, AX and Morais-de-Sa, E. Emerging Mechanisms and Roles for Asymmetric Cytokinesis. International review of cell and molecular biology. 2017;332:297-345
https://www.ncbi.nlm.nih.gov/pubmed/28526136

TEAM MEMBERS

Name	Academic degree	Professional situation	Time %
Adriana Mendes	BSc	MScstudent	100%
Ana Filipa Sobral	MSc	PhDstudent	100%
Ana Marta Silva	PhD	Posdoctoralfellow	100%
Ana X Carvalho	PhD	FCT Investigator; Group Leader	100%
Daniel Osorio	PhD	Posdoctoralfellow	100%
Fung Yi Chan	PhD	Posdoctoralfellow	100%
Inês Loureiro	PhD	Posdoctoralfellow	100%
Inês Santos	MSc	PhDstudent	100%
Joana Leite	MSc	PhDstudent	100%
Joana Saramago	MSc	PhDstudent	100%

DIFFERENTIATION & CANCER

GROUP LEADER: **Raquel Almeida**



AIM OF THE GROUP

Our general aim is to identify key molecular events and biomarkers that contribute to understand the biology of cancer and may be translated to patient care. We adopt an integrative approach using clinical specimens, cellular systems and animal models. Specifically, we aim at understanding the impact of transcriptional and post-transcriptional regulatory mechanisms in cancer initiation and progression. We aim to understand the mechanisms that drive differentiation switches, mainly in the GI tract, and how these impact cancer initiation, cancer progression and therapy resistance. Finally, we aim to understand the mechanisms that drive ovarian cancer metastization and peritoneal implantation.

MAJOR ACHIEVEMENTS IN 2017

In 2017, our major achievement was the establishment of a cellular system, using genome editing approaches that allows the precise control over CDX2 expression, a key determinant of intestinal differentiation and a biomarker of therapy response in intestinal cancer. With this approach, we have identified new CDX2 targets that may also be used as biomarkers in cancer.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Brás, OR, Cointet, J-P, Cambrosio, A, David, L, Nunes, JA, Cardoso, F and Jerónimo, C. Oncology research in late twentieth century and turn of the century Portugal: a scientometric approach to its institutional and semantic dimensions. Scientometrics. 2017;113(2):867-88
https://link.springer.com/article/10.1007/s11192-017-2491-y (Impact Factor: 2.173)
2. Pereira, B, Billaud, M and Almeida, R. RNA-Binding Proteins in Cancer: Old Players and New Actors. Trends Cancer. 2017;3(7):506-28
https://www.ncbi.nlm.nih.gov/pubmed/28718405 (Impact Factor: NA)

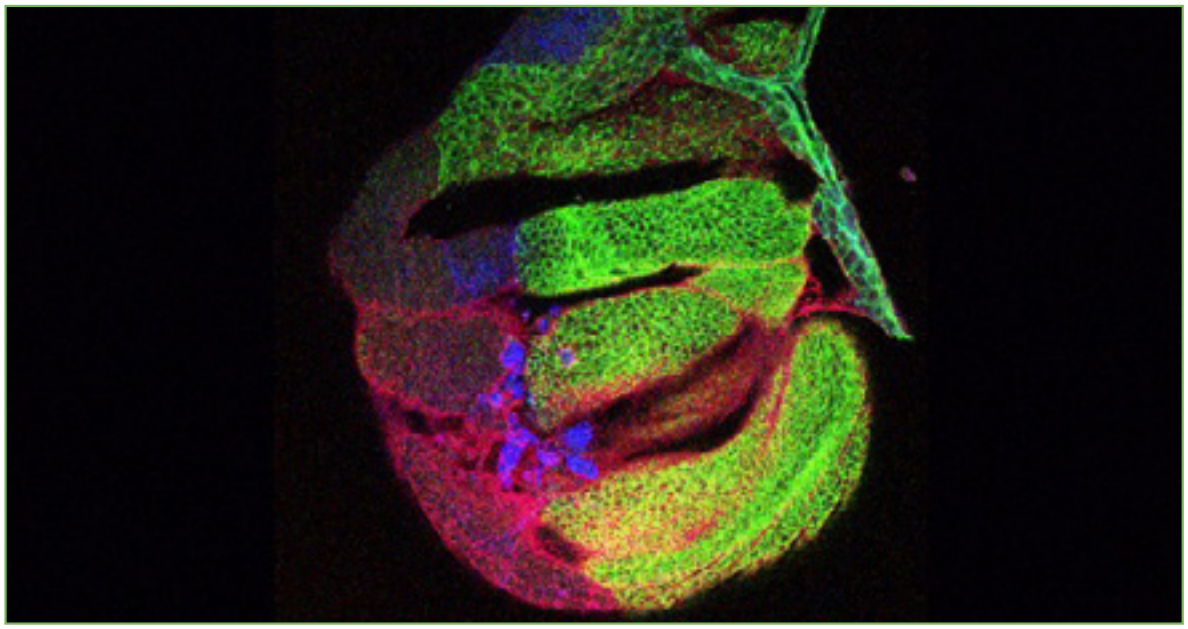
3. Pinto, R, Hansen, L, Hintze, J, Almeida, R, Larsen, S, Coskun, M, Davidsen, J, Mitchelmore, C, David, L, Troelsen, JT and Bennett, EP. Precise integration of inducible transcriptional elements (PrIITE) enables absolute control of gene expression. Nucleic acids research. 2017;45(13):e123 https://www.ncbi.nlm.nih.gov/pubmed/28472465 (Impact Factor: 11.561)
4. Rolim, I, Rodrigues, RV, Bettencourt, A, Barros, R, Camilo, V, Dias Pereira, A, Almeida, R and Chaves, P. Mid-Esophagus Columnar Metaplasia: What Is the Biopathogenic Pathway? Int J Surg Pathol. 2017;25(3):262-5 https://www.ncbi.nlm.nih.gov/pubmed/27708180 (Impact Factor: 1.188)
5. Tsai, MH, Lin, X, Shumilov, A, Bernhardt, K, Feederle, R, Poirey, R, Kopp-Schneider, A, Pereira, B, Almeida, R and Delecluse, HJ. The biological properties of different Epstein-Barr virus strains explain their association with various types of cancers. Oncotarget. 2017;8(6):10238-54 https://www.ncbi.nlm.nih.gov/pubmed/28052012 (Impact Factor: NA)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Alexandre Dias	MSc	Fellowship	Junior Researcher	100
Ana Luisa Amaral	MSc	Fellowship	Technician	100
Bruno Pereira	PhD	Fellowship	Post-doc	100
Diana Pádua	MSc	Fellowship	Junior Researcher	100
Leonor David	MD, PhD	Contract	Full Professor	100
Nair Lopes	PhD	Fellowship	Post-doc	100
Patrícia Mesquita	PhD	Contract	Researcher	100
Raquel Almeida	PhD	Contract	Researcher	100
Ricardo Coelho	MSc	Fellowship	PhD student	100
Sara Ricardo	PhD	Contract	Reseacher	100

EPITHELIAL INTERACTIONS IN CANCER

GROUP LEADER: **Raquel Seruca**



AIM OF THE GROUP

The long-term goal of the EPIC Group is to uncover how epithelial cell-cell and cell-matrix junctions, as well as the surrounding epithelial microenvironment, can influence cancer initiation and progression. Specifically, and based on common epithelial-derived cancers (gastric, breast, and colorectal), the Group will establish the contribution of adhesion molecules (E- and P-cadherins), infections (Helicobacter pylori and the microbiota), and non-neoplastic components of the tumor tissue (fibroblast-like cells, the cancer cell secreted peptides and the elements of the extracellular matrix) to alter epithelial homeostasis and cancer development.

With this goal our specific aims are:

1) In the context of gastric cancer:

- **a**) To determine the pathogenic significance of E-cadherin missense mutations in hereditary diffuse gastric cancer syndrome;
- **b**) To identify the molecular mechanisms associated to E-cadherin dysfunction and cancer cell invasion;
- **c**) To establish the role of E-cadherin in congenital malformations, namely in non-syndromic oral facial clefts (cleft lip/palate);
- **d**) To identify the key proteins involved in basal extrusion of E-cadherin negative cells within the epithelium and study the influence of normal cells in this process;
- **e**) To develop new tools to study protein expression patterns in cell populations and associated cellular features;
- **f**) To develop new assays to isolate live tumor cells based on the interaction of cancer cells with specific components of the extracellular matrix;
- **g**) To identify H. pylori bacterial virulence factors and epithelial cell signaling pathways modified by the bacteria that lead to alterations in cell-cell adhesion and modification of cell migration and invasion;
- **h**) To identify a gastric microbiome profile associated with gastric cancer.

2) In the context of breast cancer:
- **a**) To identify key proteins and signaling pathways contributing to the origin of poor prognosis basal-like breast cancer;
- **b**) To determine the metabolic cues allowing cancer stem cells (CSCs) to survive in circulation, increasing their ability to metastasize;
- **c**) To evaluate the relevance of CSC in brain metastasis;
- **d**) To identify predictive biomarkers of disease evolution and risk of brain metastasis that could be used to stratify breast cancer patients for targeted therapies;
- **e**) To develop new in vitro and in vivo models to study the paracrine interaction between breast cancer cells and the brain ECM microenvironment;

3) In the context of colorectal cancer:
- **a**) To evaluate the role of mutant KRAS in controlling cancer cell-fibroblasts crosstalk and its impact on cancer initiation and progression;
- **b**) To evaluate the role of mutant KRAS in controlling cancer cell immune escape;
- **c**) To determine the role of the tumor microenvironment in inducing cancer stem cell properties;
- **d**) To develop novel therapies for colorectal cancer patients.

MAJOR ACHIEVEMENTS IN 2017

- We proposed a new fluorescence image-based tool to determine DNA content in distinct cell cycle stages. The method is based on discriminative features, such as total intensity and area, retrieved from in situ stained nuclei by fluorescence microscopy. This tool allows determining cell cycle phase of both single and population of cells, exhibiting an overall sensitivity of 94.0%. Importantly, this novel imaging approach is a non-disruptive method that allows an integrative and simultaneous quantitative analysis of molecular and morphological parameters, thus awarding the possibility of cell cycle profiling in cytological and histological samples.
- Over the last few years, intensive research has focused on evaluating the functional consequences of germline CDH1 missense variants and in assessing E-cadherin pathogenicity. In that context, our group has contributed to better characterize CDH1 germline missense variants and is now considered a worldwide reference center. We revisited the state of the art methodologies to categorize CDH1 variants, as neutral or deleterious and, currently, this information is subsequently integrated with clinical data for genetic counseling and management of CDH1 variant carriers.
- In the context of gastric cancer, we have reviewed major aspects of its pathogenesis, genetics and molecular classifications in light of recent findings.
- In the field of H. pylori infection, we have contributed to show that H. pylori secretes a protease that cleaves several intercellular junctions and allows the bacteria to reach the basolateral domain of the host cell membrane, where the virulence factor CagA is injected into the host cell cytoplasm. We have also shown that another H. pylori virulence factor, urease, induces the expression of pro-angiogenic factors and the decrease of expression of anti-angiogenic factors by gastric epithelial cells. In vitro, H. pylori urease induces the formation of tube-like structures by human umbilical vascular endothelial cells, and in vivo, in the chicken embryo chorioallantoic membrane model, H. pylori urease induced intense neo-vascularization. In conclusion, our results indicate that besides allowing bacterial colonization of the gastric mucosa, H. pylori urease triggers processes that initiate pro-angiogenic responses in different cellular models.
- We investigated the role of F-actin in supporting the expansion of cancer precursors downstream of Src signaling. Using a breast cell line with conditional Src induction, we demonstrated that prior to cells acquiring

malignant features, they undergo a transient stress-fiber-dependent stiffening state leading to cell proliferation and the progression towards a fully transformed state. Overall, our work places actin regulation and cell rigidity as central contributors to all stages of in the evolution of breast cancer, which opens new avenues of exploration when designing cancer-targeting therapies.

- We evaluated the Prognostic value of stromal tumour infiltrating lymphocytes (TILs) and programmed cell death-ligand 1 (PDL-1) expression in breast cancer. Interestingly, we have confirmed the association of stromal TILs and PDL1 expression with aggressive forms of BC and with the clinical outcome in cases enriched for a mesenchymal immunophenotype. In conclusion, we described for the first time a close relationship between CSC markers and PDL1 expression.
- We addressed, for the first time, the expression of P-cadherin, CD44, and CD49f in primary breast carcinomas and matched axillary loco-regional metastases, in order to evaluate their impact in patients' survival. In this study, we showed that P-cadherin is an independent indicator of prognosis in the metastatic setting, being a stronger candidate biomarker for axillary-based breast cancer decisions in the clinical practice than the classical cancer stem cell markers.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Ferro, A, Mestre, T, Carneiro, P, Sahumbaiev, I, Seruca, R and Sanches, JM. Blue intensity matters for cell cycle profiling in fluorescence DAPI-stained images. Lab Invest. 2017;97(5):615-25 https://www.ncbi.nlm.nih.gov/pubmed/28263290 (Impact Factor: 4.254)
2. Figueiredo, C, Camargo, MC, Leite, M, Fuentes-Panana, EM, Rabkin, CS and Machado, JC. Pathogenesis of Gastric Cancer: Genetics and Molecular Classification. Current topics in microbiology and immunology. 2017;400:277-304 https://www.ncbi.nlm.nih.gov/pubmed/28124158 (Impact Factor: 13.843)
3. Fontenete, S, Leite, M, Figueiredo, C, Cos, P and Azevedo, NF. Detection of Helicobacter pylori in the Gastric Mucosa by Fluorescence In Vivo Hybridization. Methods Mol Biol. 2017;1616:137-46 https://www.ncbi.nlm.nih.gov/pubmed/28600766 (Impact Factor: NA)
4. Melo, S, Figueiredo, J, Fernandes, MS, Goncalves, M, Morais-de-Sa, E, Sanches, JM and Seruca, R. Predicting the Functional Impact of CDH1 Missense Mutations in Hereditary Diffuse Gastric Cancer. Int J Mol Sci. 2017;18(12) https://www.ncbi.nlm.nih.gov/pubmed/29231860 (Impact Factor: 3.687)
5. Molina-Castro, S, Pereira-Marques, J, Figueiredo, C, Machado, JC and Varon, C. Gastric cancer: Basic aspects. Helicobacter. 2017;22 Suppl 1 https://www.ncbi.nlm.nih.gov/pubmed/28891129 (Impact Factor: 4.123)
6. Olivera-Severo, D, Uberti, AF, Marques, MS, Pinto, MT, Gomez-Lazaro, M, Figueiredo, C, Leite, M and Carlini, CR. A New Role for Helicobacter pylori Urease: Contributions to Angiogenesis. Frontiers in microbiology. 2017;8:1883 https://www.ncbi.nlm.nih.gov/pubmed/29021786 (Impact Factor: 4.019)
7. Polonia, A, Pinto, R, Cameselle-Teijeiro, JF, Schmitt, FC and Paredes, J. Prognostic value of stromal tumour infiltrating lymphocytes and programmed cell death-ligand 1 expression in breast cancer. J Clin Pathol. 2017;70(10):860-7 https://www.ncbi.nlm.nih.gov/pubmed/28373294 (Impact Factor: 2.894)
8. Santos, RS, Dakwar, GR, Zagato, E, Brans, T, Figueiredo, C, Raemdonck, K, Azevedo, NF, De Smedt, SC and Braeckmans, K. Intracellular delivery of oligonucleotides in Helicobacter pylori by fusogenic liposomes in the presence of gastric mucus. Biomaterials. 2017;138:1-12 https://www.ncbi.nlm.nih.gov/pubmed/28550752 (Impact Factor: 8.806)
9. Tavares, S, Vieira, AF, Taubenberger, AV, Araujo, M, Martins, NP, Bras-Pereira, C, Polonia, A, Herbig, M, Barreto, C, Otto, O, Cardoso, J, Pereira-Leal, JB, Guck, J, Paredes, J and Janody, F. Actin stress fiber organization promotes cell stiffening and proliferation of pre-invasive breast cancer cells. Nat Commun. 2017;8:15237 https://www.ncbi.nlm.nih.gov/pubmed/28508872 (Impact Factor: 12.353)
10. Tegtmeyer, N, Wessler, S, Necchi, V, Rohde, M, Harrer, A, Rau, TT, Asche, CI, Boehm, M, Loessner, H, Figueiredo, C, Naumann, M, Palmisano, R, Solcia, E, Ricci, V and Backert, S. Helicobacter pylori Employs a Unique Basolateral Type IV Secretion Mechanism for CagA Delivery. Cell host & microbe. 2017;22(4):552-60 e5 https://www.ncbi.nlm.nih.gov/pubmed/29024645 (Impact Factor: 17.872)

11. Vieira, AF, Dionisio, MR, Gomes, M, Cameselle-Teijeiro, JF, Lacerda, M, Amendoeira, I, Schmitt, F and Paredes, J. P-cadherin: a useful biomarker for axillary-based breast cancer decisions in the clinical practice. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2017;30(5):698-709 https://www.ncbi.nlm.nih.gov/pubmed/28084338 (Impact Factor: 6.655)

Books & Book Chapters

1. Castro, P and Carneiro, P. Live-cell imaging: Seeing is believing. In: R. Seruca, J. S. Suri and J. M. Sanches, editors. Fluorescence imaging and biological quantification: CRC Press; 2017. p. 39-48
2. Fernandes, MS, Ferro, A, Carneiro, P, Seruca, R and Sanches, JM. Quantum Dots: Concepts, Imaging and Therapeutic Applications in Cancer. In: R. Seruca, J. S. Suri and J. M. Sanches, editors. Fluorescence imaging and biological quantification: CRC Press; 2017. p. 105-18.
3. Ferro, A, Carneiro, P, Fernandes, MS, Mestre, T, Sahumbaiev, I, Sanches, JM and Seruca, R. Illuminating the cycle of life. In: R. Seruca, J. S. Suri and J. M. Sanches, editors. Fluorescence imaging and biological quantification: CRC Press; 2017. p. 201-30
4. Figueiredo, C. Helicobacter heilmannii Infection. In: F. Carneiro, P. Chaves and A. Ensari, editors. Pathology of the Gastrointestinal Tract. Cham: Springer International Publishing; 2017. p. 333-6 https://doi.org/10.1007/978-3-319-40560-5_1630
5. Figueiredo, C. Helicobacter pylori Infection. In: F. Carneiro, P. Chaves and A. Ensari, editors. Pathology of the Gastrointestinal Tract. Cham: Springer International Publishing; 2017. p. 336-41 https://doi.org/10.1007/978-3-319-40560-5_1631
6. Figueiredo, C, Camargo, MC, Leite, M, Fuentes-Pananá, EM, Rabkin, CS and Machado, JC. Pathogenesis of gastric cancer: genetics and molecular classification. Molecular Pathogenesis and Signal Transduction by Helicobacter pylori: Springer; 2017. p. 277-304.
7. Figueiredo, J, Ribeiro, AS, Mestre, T, Esménio, S, Fonseca, M, Paredes, J, Seruca, R and Sanches, JM. Capturing quantitative features of protein expression from in situ fluorescence microscopic images of cancer cell populations. In: R. Seruca, J. S. Suri and J. M. Sanches, editors. Fluorescence imaging and biological quantification: CRC Press; 2017. p. 279-97.
8. Serra-Roma, A, Carvalho, PD and Velho, S. Tracking cancer: In vivo imaging techniques. In: R. Seruca, J. S. Suri and J. M. Sanches, editors. Fluorescence imaging and biological quantification: CRC Press; 2017. p. 85-104.

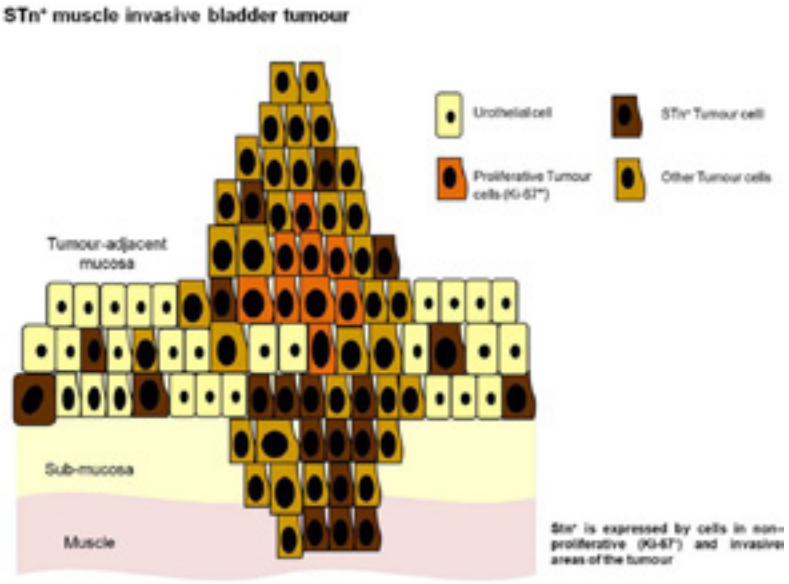
TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Luísa Machado	BSc	Master student	Master student	100
Ana Moreira	MSc	PhD fellowship	PhD student	100
Ana Sofia Ribeiro	PhD	Assistant Researcher	Assistant Researcher	100
André Vieira	PhD	Postdoctoral fellowship	Post-Doc Researcher	100
Bárbara Sousa	PhD	Postdoctoral fellowship	Post-Doc Researcher	100
Carolina Noronha	MD	PhD fellowship	PhD student	30
Céu Figueiredo	PhD	Assistant Professor	Principal investigator	60
Fernando Schmitt	MD, PhD	Associate Professor; Pathologist	Principal Investigator	30
Flávia Castro	MSc	Research fellowship	Research fellow	100
Inês Ribeiro	MSc	PhD fellowship	PhD student	100
Joana Figueiredo	PhD	Postdoctoral fellowship	Post-Doc Researcher	100
Joana Marques	MSc	PhD fellowship	PhD student	100
Joana Melo	MSc	PhD fellowship	PhD student	100
Joana Paredes	PhD	FCT Investigator	Principal investigator	100
Joana Pereira	MSc	Research fellowship	Research fellow	100
Marina Leite	PhD	Postdoctoral fellowship	Post-Doc Researcher	100
Miguel Marques	MSc	PhD fellowship	PhD student	100
Mónica Oliveira	MSc	Research fellowship	Research fellow	100
Patrícia Carneiro	PhD	Assistant Researcher	Assistant Researcher	100

Name	Academic degree	Professional situation	Category/Position	Time %
Patrícia Carvalho	MSc	PhD fellowship	PhD student	100
Raquel Seruca	MD, PhD	Group leader; Vice-president, Ipatimup; Coordinator, i3S Cancer program	Principal investigator	100
Rita Canário	MD	PhD fellowship	PhD student	100
Rita Carvalho	MSc	PhD fellowship	PhD student	100
Rui Ferreira	PhD	Postdoctoral fellowship	Post-Doc Researcher	100
Sérgia Velho	PhD	FCT Investigator	Assistant Researcher	100
Sofia Fernades	PhD	Assistant Researcher	Assistant Researcher	100
Soraia Melo	MSc	PhD fellowship	PhD student	100
Susana Mendonça	MSc	Research fellowship	Research fellow	100
Tânia Fernandes	MSc	Research fellowship	Research fellow	100
Vanessa Pinto	MSc	Research fellowship	Research fellow	100

EXPERIMENTAL PATHOLOGY AND THERAPEUTICS

GROUP LEADER: **Lúcio Lara Santos**



AIM OF THE GROUP

The Experimental Pathology and Therapeutics Group, established in 2008 as one of the research groups of the IPO PORTO FG EPE, is currently coordinated by Professor Lúcio Santos (MD PhD). The group is currently includes 9 senior researchers (Phd level), 12 Phd students and 2 Msc student and 3 collaborators. The group also provides a solid platform for training and higher education in cancer research. Reflecting this commitment, over the past four years the group has welcomed several post-graduate students from the University of Aveiro, Porto, Coimbra, Minho and UTAD as well as international students from Angola. The group is also involved in GlyCoCan, a Marie Curie European Training Network composed of 15 leading European partners in the fields of glycobiology, glyco-immunology and biomarker research. It provides a multidisciplinary training for a new generation of researchers in the young field of glyco-oncology, bridging academic and industrial sectors.

The Experimental Pathology and Therapeutics group will devote the efforts of the next years to both basic and translational cancer research with the purpose of identifying glycobiomarkers for early detection of the disease, prognosis, drug response and to guide therapeutic decision. Ultimately it will also focus on translating this knowledge into novel therapeutics. One of the main goal for 2018-2022 is to determine the clinical relevance of circulating tumor cells (CTC) expressing the short chain O-glycan, STn, in gatrointestinal tumors using an innovative microfluidics device and development of CTC ex vivo models for individualized testing drug susceptibility. Regarding target therapeutics, the goal is to identify specific CD44 glycoforms and develop specific ligands for CAR-T therapeutics and antibody development for glycan-based nanotherapeutics for cancer for this study. Other study line will be the implementation of a immunological profile of patients who are candidates for therapeutic approaches in the field of immunology and the development of strategies for dendritic cell stimulation.

MAJOR ACHIEVEMENTS IN 2017

- Azevedo R, Peixoto A, Gaiteiro C, Fernandes E, Neves M, Lima L, Santos LL, Ferreira JA: Over forty years of bladder cancer glycobiology: Where do glycans stand facing precision oncology? Oncotarget 2017, 8(53):91734-91764. Impact factor: 5.168.
- Cotton S, Azevedo R, Gaiteiro C, Ferreira D, Lima L, Peixoto A, Fernandes E, Neves M, Neves D, Amaro T, Cruz R, Tavares A, Rangel M, Silva AMN, Santos LL, Ferreira JA: Targeted O-glycoproteomics explored increased sialylation and identified MUC16 as a poor prognosis biomarker in advanced-stage bladder tumours. Mol Oncol 2017, 11(8):895-912. Impact factor: 5.314.
- Lima L, Neves M, Oliveira MI, Dieguez L, Freitas R, Azevedo R, Gaiteiro C, Soares J, Ferreira D, Peixoto A, Fernandes E, Montezuma D, Tavares A, Ribeiro R, Castro A, Oliveira M, Fraga A, Reis CA, Santos LL, Ferreira JA: Sialyl-Tn identifies muscle-invasive bladder cancer basal and luminal subtypes facing decreased survival, being expressed by circulating tumor cells and metastases. Urologic oncology 2017, 35(12):675 e671-675 e678. Impact factor: 3.767.
- Ferreira JA, Magalhaes A, Gomes J, Peixoto A, Gaiteiro C, Fernandes E, Santos LL, Reis CA: Protein glycosylation in gastric and colorectal cancers: Toward cancer detection and targeted therapeutics. Cancer Lett 2017, 387:32-45. Impact factor: 6.375.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Alvarado, A, Gil da Costa, RM, Faustino-Rocha, AI, Ferreira, R, Lopes, C, Oliveira, PA and Colaco, B. Effects of exercise training on breast cancer metastasis in a rat model. International journal of experimental pathology. 2017;98(1):40-6 http://www.ncbi.nlm.nih.gov/pubmed/28556395 (Impact Factor: 1.938)
2. Antunes, L, Santos, LL and Bento, MJ. Survival from cancer in the north region of Portugal: results from the first decade of the millennium. European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation. 2017;26 Joining forces for better cancer registration in Europe:S170-S5 http://www.ncbi.nlm.nih.gov/pubmed/28590274 (Impact Factor: 2.886)
3. Azevedo, R, Peixoto, A, Gaiteiro, C, Fernandes, E, Neves, M, Lima, L, Santos, LL and Ferreira, JA. Over forty years of bladder cancer glycobiology: Where do glycans stand facing precision oncology? Oncotarget. 2017;8(53):91734-64 https://www.ncbi.nlm.nih.gov/pubmed/29207682 (Impact Factor: NA)
4. Barbosa, J, Faria, J, Leal, S, Afonso, LP, Lobo, J, Queiros, O, Moreira, R, Carvalho, F and Dinis-Oliveira, RJ. Acute administration of tramadol and tapentadol at effective analgesic and maximum tolerated doses causes hepato- and nephrotoxic effects in Wistar rats. Toxicology. 2017;389:118-29 https://www.ncbi.nlm.nih.gov/pubmed/28689766 (Impact Factor: 3.265)
5. Cotton, S, Azevedo, R, Gaiteiro, C, Ferreira, D, Lima, L, Peixoto, A, Fernandes, E, Neves, M, Neves, D, Amaro, T, Cruz, R, Tavares, A, Rangel, M, Silva, AMN, Santos, LL and Ferreira, JA. Targeted O-glycoproteomics explored increased sialylation and identified MUC16 as a poor prognosis biomarker in advanced-stage bladder tumours. Molecular oncology. 2017;11(8):895-912 https://www.ncbi.nlm.nih.gov/pubmed/28156048 (Impact Factor: 5.264)
6. Da Cruz Paula, A, Leitao, C, Marques, O, Rosa, AM, Santos, AH, Rema, A, de Fatima Faria, M, Rocha, A, Costa, JL, Lima, M and Lopes, C. Molecular characterization of CD44(+)/CD24(-)/Ck(+)/CD45(-) cells in benign and malignant breast lesions. Virchows Arch. 2017;470(3):311-22 https://www.ncbi.nlm.nih.gov/pubmed/28116522 (Impact Factor: 2.936)
7. Da Cruz Paula, A and Lopes, C. Implications of Different Cancer Stem Cell Phenotypes in Breast Cancer. Anticancer Res. 2017;37(5):2173-83 http://www.ncbi.nlm.nih.gov/pubmed/28476780 (Impact Factor: 1.865)
8. Dias Bastos, PA, Vlahou, A, Leite-Moreira, A, Santos, LL, Ferreira, R and Vitorino, R. Deciphering the disease-related molecular networks using urine proteomics. TrAC Trends in Analytical Chemistry. 2017;94:200-9 http://www.sciencedirect.com/science/article/pii/S0165993616302126 (Impact Factor: 7.034)
9. Faria, J, Barbosa, J, Leal, S, Afonso, LP, Lobo, J, Moreira, R, Queiros, O, Carvalho, F and Dinis-Oliveira, RJ. Effective analgesic doses of tramadol or tapentadol induce brain, lung and heart toxicity in Wistar rats. Toxicology. 2017;385:38-47 https://www.ncbi.nlm.nih.gov/pubmed/28499616 (Impact Factor: 3.265)

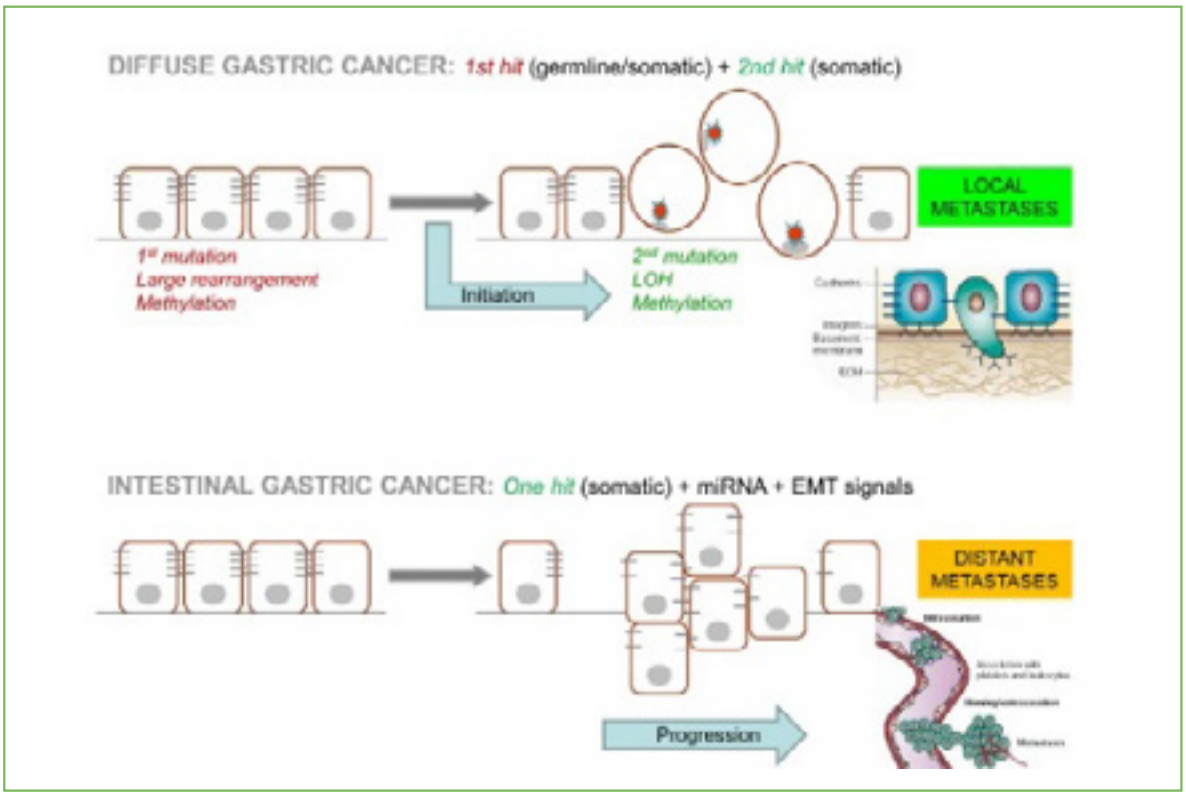
10. Ferreira, JA, Magalhaes, A, Gomes, J, Peixoto, A, Gaiteiro, C, Fernandes, E, Santos, LL and Reis, CA. Protein glycosylation in gastric and colorectal cancers: Toward cancer detection and targeted therapeutics. Cancer letters. 2017;387:32-45 https://www.ncbi.nlm.nih.gov/pubmed/26828132 (Impact Factor: 6.491)
11. Fraga, A, Ribeiro, R, Coelho, A, Vizcaino, JR, Coutinho, H, Lopes, JM, Principe, P, Lobato, C, Lopes, C and Medeiros, R. Genetic polymorphisms in key hypoxia-regulated downstream molecules and phenotypic correlation in prostate cancer. BMC urology. 2017;17(1):12 https://www.ncbi.nlm.nih.gov/pubmed/28143503 (Impact Factor: 1.792)
12. Gil da Costa, RM, Aragao, S, Moutinho, M, Alvarado, A, Carmo, D, Casaca, F, Silva, S, Ribeiro, J, Sousa, H, Ferreira, R, Nogueira-Ferreira, R, Pires, MJ, Colaco, B, Medeiros, R, Venancio, C, Oliveira, MM, Bastos, MM, Lopes, C and Oliveira, PA. HPV16 induces a wasting syndrome in transgenic mice: Amelioration by dietary polyphenols via NF-kappaB inhibition. Life Sci. 2017;169:11-9 http://www.ncbi.nlm.nih.gov/pubmed/27888116 (Impact Factor: 3.234)
13. Gouveia, MJ, Pakharukova, MY, Laha, T, Sripa, B, Maksimova, GA, Rinaldi, G, Brindley, PJ, Mordvinov, VA, Amaro, T, Santos, LL, Costa, J and Vale, N. Infection with Opisthorchis felineus induces intraepithelial neoplasia of the biliary tract in a rodent model. Carcinogenesis. 2017;38(9):929-37 http://www.ncbi.nlm.nih.gov/pubmed/28910999 (Impact Factor: 5.072)
14. Lima, L, Neves, M, Oliveira, MI, Dieguez, L, Freitas, R, Azevedo, R, Gaiteiro, C, Soares, J, Ferreira, D, Peixoto, A, Fernandes, E, Montezuma, D, Tavares, A, Ribeiro, R, Castro, A, Oliveira, M, Fraga, A, Reis, CA, Santos, LL and Ferreira, JA. Sialyl-Tn identifies muscle-invasive bladder cancer basal and luminal subtypes facing decreased survival, being expressed by circulating tumor cells and metastases. Urologic oncology. 2017;35(12):675 e1- e8 https://www.ncbi.nlm.nih.gov/pubmed/28911924 (Impact Factor: 3.397)
15. Lind, AL, Wisecaver, JH, Lameiras, C, Wiemann, P, Palmer, JM, Keller, NP, Rodrigues, F, Goldman, GH and Rokas, A. Drivers of genetic diversity in secondary metabolic gene clusters within a fungal species. PLoS Biol. 2017;15(11):e2003583 http://www.ncbi.nlm.nih.gov/pubmed/29149178 (Impact Factor: 9.163)
16. Miguel, F, Lopes, LV, Ferreira, E, Ribas, E, Pelaez, AF, Leal, C, Amaro, T, Lopes, P, Santos, CM, Lopes, C and Santos, LL. Breast cancer in Angola, molecular subtypes: a first glance. Ecancermedicalscience. 2017;11:763 http://www.ncbi.nlm.nih.gov/pubmed/28900476 (Impact Factor: NA)
17. Padrao, AI, Figueira, AC, Faustino-Rocha, AI, Gama, A, Loureiro, MM, Neuparth, MJ, Moreira-Goncalves, D, Vitorino, R, Amado, F, Santos, LL, Oliveira, PA, Duarte, JA and Ferreira, R. Long-term exercise training prevents mammary tumorigenesis-induced muscle wasting in rats through the regulation of TWEAK signalling. Acta physiologica. 2017;219(4):803-13 https://www.ncbi.nlm.nih.gov/pubmed/27228549 (Impact Factor: 27.125)
18. Da Costa, RMG, Araujo, R, Santos, JMO, Fernandes, M, Neto, T, Sousa, H, Ribeiro, J, Bastos, M, Oliveira, PA, Carmo, D, Casaca, F, Silva, S, Lopes, C and Medeiros, R. Regulation of miRNA-146a and miRNA-150 Levels by Celecoxib in Premalignant Lesions of K14-HPV16 Mice. Anticancer Res. 2017;37(6):2913-8 http://www.ncbi.nlm.nih.gov/pubmed/28551628 (Impact Factor: 1.865)
19. Santos, MD, Silva, C, Rocha, A, Nogueira, C, Castro-Pocas, F, Araujo, A, Matos, E, Pereira, C, Medeiros, R and Lopes, C. Prognostic and Therapeutic Potential Implications of Genetic Variability in Prostaglandin E2 Pathway Genes in Rectal Cancer. Anticancer Res. 2017;37(1):281-91 http://www.ncbi.nlm.nih.gov/pubmed/28011504 (Impact Factor: 1.865)
20. Santos, MD, Silva, C, Rocha, A, Nogueira, C, Castro-Pocas, F, Araujo, A, Matos, E, Pereira, C, Medeiros, R and Lopes, C. Predictive clinical model of tumor response after chemoradiation in rectal cancer. Oncotarget. 2017;8(35):58133-51 http://www.ncbi.nlm.nih.gov/pubmed/28938543 (Impact Factor: NA)
21. Silva, J, Arantes-Rodrigues, R, Pinto-Leite, R, Faustino-Rocha, AI, Fidalgo-Goncalves, L, Santos, L and Oliveira, PA. Synergistic Effect of Carboplatin and Piroxicam on Two Bladder Cancer Cell Lines. Anticancer Res. 2017;37(4):1737-45 http://www.ncbi.nlm.nih.gov/pubmed/28373436 (Impact Factor: 1.865)
22. Vale, N, Gouveia, MJ, Rinaldi, G, Santos, J, Santos, LL, Brindley, PJ and da Costa, JM. The role of estradiol metabolism in urogenital schistosomiasis-induced bladder cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2017;39(3):1010428317692247 http://www.ncbi.nlm.nih.gov/pubmed/28345469 (Impact Factor: NA)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana da Conceição Saraiva e Sousa Tavares	MSc	Employed IPO	Technician	20
Ana Rita Pereira Azevedo	MSc	Scholarship	PhD student	100
Carina Susana Diogo Bernardo	PhD	Scholarship	Scholarship	100
Carlos Alberto da Silva Lopes	Aggregation	Retired	Jubilated Professor	30
Carlos Alberto Palmeira de Sousa	PhD	Employed IPO	Clinical Scientist	30
Catarina Reis Almeida Lameiras	MSc	Employed IPO	Clinical Scientist	20
Cristiana Milhazes Gaiteiro	MSc	Scholarship	PhD student	100
Cristina Freitas Carvalho Sousa Pinto	PhD	Employed ESEP	Nurse	30
Dora Maria Barrocas Bernardo	MSc	Employed IPO	PhD student	100
Elisabete Cristina Nunes Fernandes	MSc	Scholarship	PhD student	60
José Alexandre Ribeiro de Castro Ferreira	PhD	Scholarship	Post-Doc Researcher	40
Lúcio José de Lara Santos	PhD	Employed IPO	MD	30
Luís Carlos Oliveira Lima	PhD	Scholarship	Post-Doc Researcher	100
Luís Pedro Fernandes Afonso	BSc	Employed IPO	MD	20
Manuel Filipe Teles Neves	MSc	Scholarship	PhD student	100
Maria do Rosário Lima Viseu de Carvalho Pinto Leite	PhD	Employed HVR	Clinical Scientist	30
Andreia Filipa Ferreira Peixoto	MSc	Scholarship	PhD Student	80
Sofia do Rosário Alves Pereira	PhD	Employed UFP	Assistant Professor	10
Maria do Céu dos Santos Silva Costa	PhD	Employed UFP	Assistant Professor	20
Sofia Ribeiro Cotton	MSc	Scholarship	PhD student	100
Eliana Janine de Paiva Soares	BSc	Student	MSc Student	100
Dylan Gomes Ferreira	BSc	Scholarship	MSc Student	100
Patrick Joel da Silva Pais	MSc	Scholarship		
Roberta Zoppi	MSc		PhD student	

EXPRESSION REGULATION IN CANCER

GROUP LEADER: **Carla Oliveira**



AIM OF THE GROUP

The Expression Regulation in Cancer group (ERiC) aims to identify inherited high/moderate risk alleles that increase the likelihood of cancer development in families with gastric cancer aggregation, in order to boost the effectiveness of predictive testing and improve disease prevention. Fully aware of that goal, our dedicated team has identified novel germline alterations that increase the risk for hereditary gastric cancer, and that are used worldwide to diagnose the Hereditary Diffuse Gastric Cancer syndrome. These findings provided the requested international visibility to the team needed to integrate The European Reference Network on Genetic Tumour risk syndromes (ERN-Genturis). As a consequence, the team has became the sole Portuguese partner in a large European-wide research project (SOLVE-RD), which intends to implement an innovative brokerage structure connecting clinicians, basic and applied researchers to discoverer the missing heritability of many hereditary cancers. Our collaborations worldwide allowed us to gather and genetically explore 500 families with familial gastric cancer lacking a known germline cause.

The ERiC group has also studied clinical, molecular and next-generation sequencing data from tumours from large cohorts of gastrointestinal cancers and defined predictors of poor survival among gastric cancer patients, as well as predictive markers of therapy response in gastric and colorectal cancers. These findings and associated patients series created the background for a new objective, which is identifying circulating biomarkers for cancer detection, disease monitoring and relapse prediction. In this field of research, the team

has had important networking activities such as the participation in the management Committee of the COST action “Microvesicles and Exosomes in Health & Disease”, and later as partner in a Marie Skłodowska-Curie Innovative Training Networks “Training in Extracellular vesicles: for benefit in Health & Disease” [TRAIN-EV].

With privileged access to homogeneous patients and control cohorts, genomics, bioinformatics, and imaging associated with wet lab approaches and animal experimentation, we aimed at building topographic maps of actionable molecular alterations, and therapy resistance-associated molecular profiles in gastric cancer. To attain this aim, we engaged as part of three large National Consortium funded by Portugal, one involved in the Cancel Stem” project, another involved in the “CANCER” project and the last involved in the “DOCnet” project.

Furthermore, we often carry out joint research with our fellow i3S scientists, scientists at IMM and IGC in Lisbon, INL in Braga, and at CNC in Coimbra, while keeping in mind the ultimate translational nature of our work, so we also maintain a tight connection to hospitals in Porto, such as CHSJ, CHP and IPO-Porto, IPO-Lisboa and IPO-Coimbra. Our collaborative network goes beyond borders, comprising in Europe more than 30 institutions from 10 different countries, and research team from North America, Canada, Japan and New Zealand.

The resident Group members in 2017 consisted in the Group Leader, two Assistant researchers, three Post-doc researchers, four PhD students, two Masters students, four Technicians and a Lab Manager.

MAJOR ACHIEVEMENTS IN 2017

- We developed a new photoimmunoconjugate by conjugating a porphyrin with trastuzumab (Trast:Porph) for targeted photodynamic therapy in HER2-positive gastric cancer. In the setting of human disease, our in vitro and in vivo data suggest that repetitive cycles of Trast:Porph photoimmunotherapy may be used as an improved treatment strategy in HER2-positive gastric cancer patients.
- We performed germline whole-exome sequencing in 53 families with genetically unexplained diffuse-type and intestinal-type gastric cancer to identify novel GC-predisposing candidate genes. Despite a rigorous search, no obvious candidate predisposition genes were identified. The lack of causative mutations in the coding genome highlights the need to study regulatory elements in order to find novel disease-associated mechanisms in hereditary gastric cancer. This is the current aim of the ERiC team.
- We collaborated in the development of a rotary orbital hydrodynamic culture system applied to single-cell suspensions, to obtain homogeneously-sized cellular aggregates. The features of this culture system are important to consider when testing regenerative therapies, biomaterial development or pharmacological screening.
- We reviewed the morphological, immunophenotypic, and molecular heterogeneity in gastric cancer as the basis to better understanding this disease. The compilation of this information and the discussion of its practical implications are highly relevant for diagnostic pathology, prognostic evaluation, and precision therapy.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Korsak, B, Almeida, GM, Rocha, S, Pereira, C, Mendes, N, Osorio, H, Pereira, PMR, Rodrigues, JMM, Schneider, RJ, Sarmento, B, Tome, JPC and Oliveira, C. Porphyrin modified trastuzumab improves efficacy of HER2 targeted photodynamic therapy of gastric cancer. International journal of cancer. Journal international du cancer. 2017;141(7):1478-89 https://www.ncbi.nlm.nih.gov/pubmed/28639285 (Impact factor: 7.36)
2. Kennedy, PJ, Oliveira, C, Granja, PL and Sarmento, B. Antibodies and associates: Partners in targeted drug delivery. Pharmacol Ther. 2017;177:129-45 https://www.ncbi.nlm.nih.gov/pubmed/28315359 (Impact factor: 10.376)

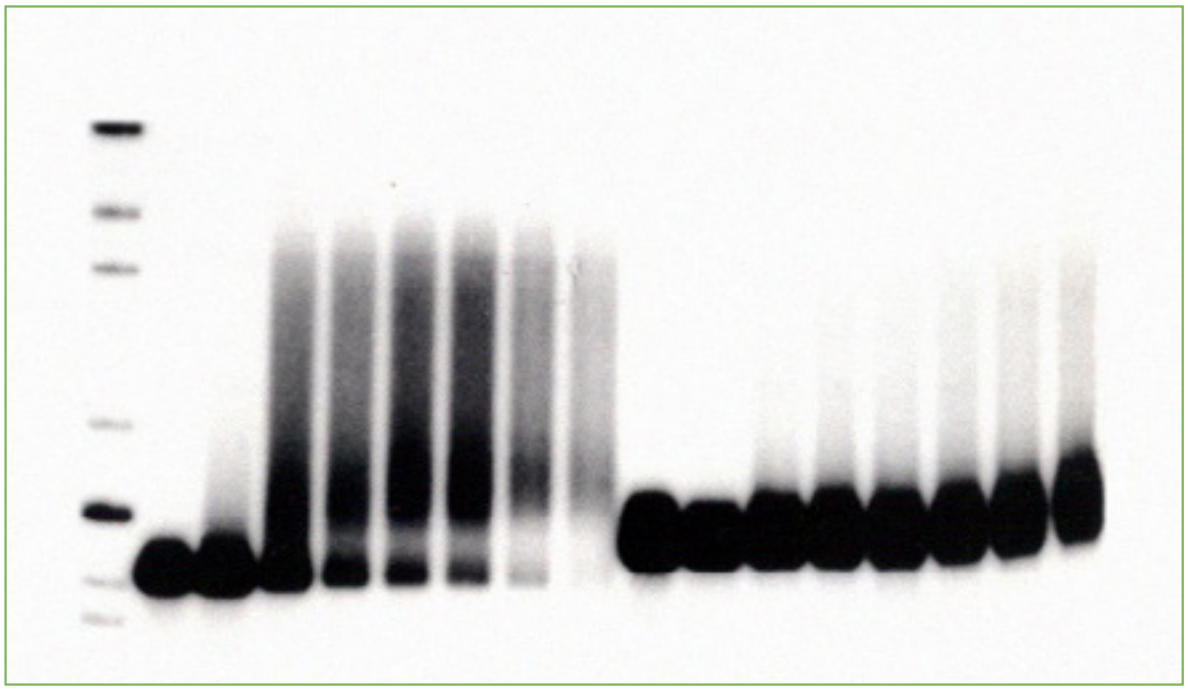
3. Vogelaar, IP, van der Post, RS, van Krieken, JHJ, Spruijt, L, van Zelst-Stams, WA, Kets, CM, Lubinski, J, Jakubowska, A, Teodorczyk, U, Aalfs, CM, van Hest, LP, Pinheiro, H, Oliveira, C, Jhangiani, SN, Muzny, DM, Gibbs, RA, Lupski, JR, de Ligt, J, Vissers, L, Hoischen, A, Gilissen, C, van de Vorst, M, Goeman, JJ, Schackert, HK, Ranzani, GN, Molinaro, V, Gomez Garcia, EB, Hes, FJ, Holinski-Feder, E, Genuardi, M, Ausems, M, Sijmons, RH, Wagner, A, van der Kolk, LE, Bjornevoll, I, Hoberg-Vetti, H, van Kessel, AG, Kuiper, RP, Ligtenberg, MJL and Hoogerbrugge, N. Unraveling genetic predisposition to familial or early onset gastric cancer using germline whole-exome sequencing. European journal of human genetics : EJHG. 2017;25(11):1246-52
https://www.ncbi.nlm.nih.gov/pubmed/28875981 (Impact factor: 3.636)
4. Laundos, TL, Silva, J, Assuncao, M, Quelhas, P, Monteiro, C, Oliveira, C, Oliveira, MJ, Pego, AP and Amaral, IF. Rotary orbital suspension culture of embryonic stem cell-derived neural stem/progenitor cells: impact of hydrodynamic culture on aggregate yield, morphology and cell phenotype. J Tissue Eng Regen Med. 2017;11(8):2227-40
https://www.ncbi.nlm.nih.gov/pubmed/26880706 (Impact factor: 1.216)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Abel Sousa	MSc	Students	PhD student	50%
Ana André	PhD	Post-doc fellow	Lab manager	100%
Anabela Ferro	PhD	Post-doc fellow	Post-doc Researcher	100%
Bárbara Mesquita	MSc	Research Fellow	Research Fellowship (MSc)	100%
Carla Oliveira	PhD	Tenure track	Principal Researcher	100%
Carla Pereira	MSc	Student	PhD Student	100%
Diana Lemos	BSc	Research Fellow	Research Fellowship (MSc)	100%
Gabriela Almeida	PhD	Full Time - iFCT	Assistant Researcher	100%
Irene Gullo	MD	Student	PhD Student	60%
Joana Carvalho	PhD	Post-doc fellow	Post-doc Researcher	100 %
Marlene Gil	BSc	Research Fellow	Research Fellowship (BSc)	100%
Marta Ferreira	MSc	Research Technician	Staff	100 %
Marta Moreno	BSc	Students	MSc student	50%
Patrícia Oliveira	PhD	Post-Doc Researcher	Post-Doc Researcher	100%
Pedro Ferreira	PhD	Full time - iFCT	Assistant Researcher	100%
Sara Rocha	MSc	Student	PhD Student	100%
Sara Teles	BSc	Student	MSc Student	100%

GENE REGULATION

GROUP LEADER: **Alexandra Moreira**



AIM OF THE GROUP

Many genes go through alternative pre-mRNA processing – splicing and polyadenylation - in different physiological conditions, with important implications in health and disease. Some of the fundamental question that remain unanswered and that we address in our group is how the cell chooses one polyA signal or a splicing signal instead of another in biologically relevant genes, and how is this selection regulated and integrated with RNAPII transcription.

The main objective of the group is to understand and elucidate co- and post-transcriptional molecular mechanisms involved in regulating gene expression. We focus on the molecular mechanisms involved in mRNA 3' end formation and alternative polyadenylation, with a specific interest in inflammatory and cancer cells. We mainly use molecular biology methodologies and take advantage of different model systems, in particular Drosophila melanogaster and human cells.

MAJOR ACHIEVEMENTS IN 2017

- Liu, X*, Freitas, J*, Hoque, M, Oliveira, MS, Martins, T, Henriques, T, Tian, B, and Moreira, A (2017) Transcription elongation has a tissue-specific impact in alternative cleavage and polyadenylation in Drosophila melanogaster, RNA, 23(12):1807-1816 doi:10.1261/rna.062661.117
- Rodrigues, PM, Ribeiro, AR, Perrod, C, Araújo, L, Landry, JJM, Benes, V, Pereira-Castro, I, Moreira, A, Xavier-Ferreira, H, Meireles, C and Alves, NL (2017) Thymic epithelial cells require p53 to support their long-term function in thymopoiesis in mice, Blood, 130(4):478-488. doi: 10.1182/blood-2016-12-758961

- Nogueira*, E, Freitas*, J, Loureiro, A, Nogueira, P, Gomes, AC, Preto, A, Carmo, AM, Moreira, A and Cavaco-Paulo, A (2017) Neutral PEGylated liposomal formulation for efficient folate-mediated delivery of MCL1 siRNA to activated macrophages, Colloids and Surfaces B: Biointerfaces, 155: 459–465
- Braz SO, Cruz A, Lobo A, Bravo J, Moreira-Ribeiro J, Pereira-Castro I, Freitas J, Relvas JB, Summavielle T and Moreira A (2017) Expression of Rac1 alternative 3′ UTRs is a cell specific mechanism with a function in dendrite outgrowth in cortical neurons, Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms, 1860(6):685-694. doi: 10.1016/j.bbagrm.2017.03.002

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

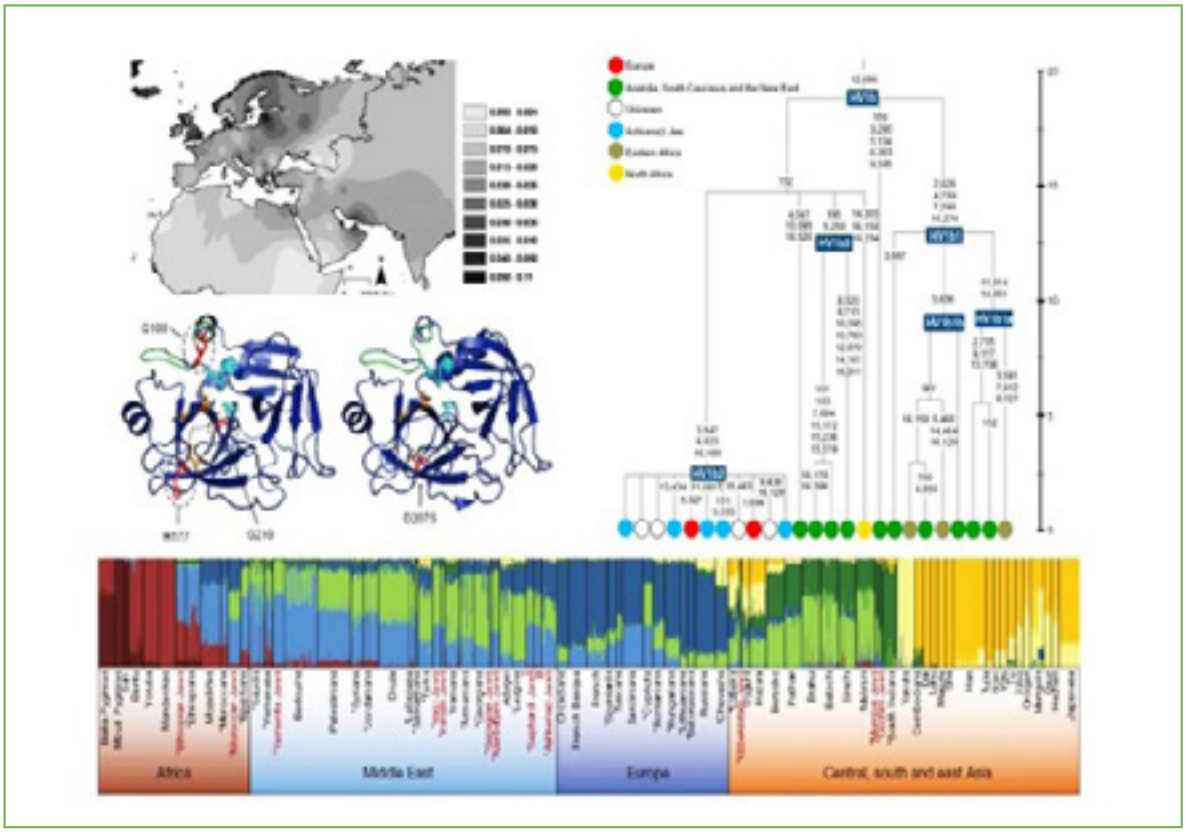
1. Liu, X, Freitas, J, Zheng, D, Oliveira, MS, Hoque, M, Martins, T, Henriques, T, Tian, B and Moreira, A. Transcription elongation rate has a tissue-specific impact on alternative cleavage and polyadenylation in Drosophila melanogaster. RNA. 2017;23(12):1807-16
   https://www.ncbi.nlm.nih.gov/pubmed/28851752 (Impact Factor: 4.49)
2. Rodrigues, PM, Ribeiro, AR, Perrod, C, Landry, JJM, Araujo, L, Pereira-Castro, I, Benes, V, Moreira, A, Xavier-Ferreira, H, Meireles, C and Alves, NL. Thymic epithelial cells require p53 to support their long-term function in thymopoiesis in mice. Blood. 2017;130(4):478-88
   https://www.ncbi.nlm.nih.gov/pubmed/28559356 (Impact Factor: 15.132)
3. Nogueira, E, Freitas, J, Loureiro, A, Nogueira, P, Gomes, AC, Preto, A, Carmo, AM, Moreira, A and Cavaco-Paulo, A. Neutral PEGylated liposomal formulation for efficient folate-mediated delivery of MCL1 siRNA to activated macrophages. Colloids Surf B Biointerfaces. 2017;155:459-65
   https://www.ncbi.nlm.nih.gov/pubmed/28472749 (Impact Factor: 3.997)
4. Braz, SO, Cruz, A, Lobo, A, Bravo, J, Moreira-Ribeiro, J, Pereira-Castro, I, Freitas, J, Relvas, JB, Summavielle, T and Moreira, A. Expression of Rac1 alternative 3' UTRs is a cell specific mechanism with a function in dendrite outgrowth in cortical neurons. Biochimica et biophysica acta. 2017;1860(6):685-94
   https://www.ncbi.nlm.nih.gov/pubmed/28274785 (Impact Factor: 5.179)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Alexandra Moreira	D.Phil	Principal Investigator	Group leader	100
Ana Jesus	MSc	Technician - Norte	Technician	100
Isabel Castro	PhD	Post-doc fellow - FCT	Post-doc	100
Jaime Freitas	PhD	Post-doc fellow – EU-Horizon project	Post-doc	100
Joana Azevedo	Undergrade	Non-paid Student	Trainee	100
Joana Wilton	MSc	PhD student – FCT fellowship	PhD student	100
Marta Oliveira	MSc	PhD student – FCT fellowship	PhD student	100
Olena Kutsenko	BSc	Master student	Master student	100

GENETIC DIVERSITY

GROUP LEADER: **Luísa Pereira**



AIM OF THE GROUP

The group establishes a bridge between human population and clinical genetics. We study drift, migration, expansion, bottleneck and selection, which model the genetic diversity. This evolutionary framework is applied to identify candidate genes/variants conferring susceptibility to diseases. Our work involves collaborations with anthropologists, statisticians, bioinformaticians and clinicians.

We are surveying genome-wide chips and whole exome/genome sequences in population samples and in case-control cohorts. These allow unbiased overall evaluations of global human evolution and of candidate genes contributing to complex diseases, respectively. We are particularly interested in investigating how ancestry leads to differential susceptibility to complex diseases. Our current disease models are dengue fever and gastric cancer, and in both African ancestry seems to play a protective role against the worse phenotypes.

We have a long track-record in the study of proteolysis related genes, especially in the context of a common European Mendelian disease, alpha1-antitrypsin deficiency. In addition, we are enlarging our focus in other lung disorders, including Chronic Obstructive Pulmonary Diseases and lung cancer, by applying genomic and proteomic approaches. We are also exploring the involvement of these genes in reproductive biology and in immune response against pathogens, using the seminal hyperviscosity phenotype in male infertility as a model.

We are internationally recognised by our work in the phylogenetic characterisation of worldwide mitochondrial DNA diversity. As mitochondria play major roles in many life-sustaining functions, they have been implicated in many complex phenotypes, including cancer. We have shown that a proper phylogenetic contextualisation is essential to disentangle between neutral and pathologic variants, and we are currently using this information in researching the cross-talk between the mitochondrial and nuclear genomes.

MAJOR ACHIEVEMENTS IN 2017

- Bantu languages are spoken by about 310 million Africans, yet the genetic history of Bantu-speaking populations remains largely unexplored. We generated genomic data for 1318 individuals from 35 populations in western central Africa, where Bantu languages originated. We found that early Bantu speakers first moved southward, through the equatorial rainforest, before spreading toward eastern and southern Africa. Genetic adaptation of Bantu speakers was facilitated by admixture with local populations, particularly for the HLA and LCT loci. Finally, we identified a major contribution of western central African Bantu speakers to the ancestry of African Americans, whose genomes present no strong signals of natural selection.
- Ethnic groups display differential genetic susceptibility to infectious diseases, such as dengue disease for which African ancestry may be protective against the haemorrhagic phenotype. A Cuban dengue fever cohort was genotyped for 2.5 million SNPs, leading to identify OSBPL10 and RXRA candidate genes, with most significant SNPs placed in enhancers, promoters and lncRNAs. Their expression was confirmed to change through dengue disease progression in Cuban patients, and knockdown of OSBPL10 expression followed by DENV2 infection led to a significant reduction in DENV replication. These genes interact in the LXR/RXR activation pathway that integrates lipid metabolism and immune functions, being a key player in dengue virus entrance into cells, its replication therein and in cytokine production.
- Large artery atherosclerotic stroke (LAS) shows substantial heritability not yet explained. The genotyping of the HumanExome BeadChip in 3,127 cases and 9,778 controls from Europe, Australia, and South Asia identified the association with a nonsynonymous single-nucleotide variant in serpin family A member 1 (SERPINA1) encoding alpha-1 antitrypsin [AAT; p.V213A; P = 5.99E-9, odds ratio (OR) = 1.22]. Using quantitative microscale thermophoresis and hydrogen/deuterium exchange combined with mass spectrometry we observed stronger interaction with lipoproteins in plasma and reduced global flexibility of the Val-213 variant that most likely improve its local availability and reduce the extent of proteolytic inactivation by other proteases in atherosclerotic plaques. Collectively, our findings point to a functionally relevant balance between lipoproteins, proteases, and AAT in atherosclerosis.
- Lung cancer is one of the deadliest types of cancer. We performed a detailed mass spectrometry based proteome analysis of acellular bronchoalveolar lavage (BAL) fluid samples on an observational prospective cohort consisting of 90 suspected lung cancer cases which were followed during two years. The thirteen new lung cancer cases diagnosed during the follow up time period clustered with lung cancer cases. Hundred and thirty-tree potential biomarkers were identified showing significantly differential expression when comparing lung cancer versus non-lung cancer. The regulated biomarkers showed a large overlap with biomarkers detected in tissue samples.
- Important gaps remain in understanding the spread of farming into Europe. By dating mitogenome founder lineages from the Near East in different regions of Europe, we found that whereas the lineages date mainly to the Neolithic in central Europe and Iberia, they largely date to the Late Glacial period in central/eastern Mediterranean Europe. This supports a scenario in which the genetic pool of Mediterranean Europe was partly a result of Late Glacial expansions from a Near Eastern refuge, and that this was an important source pool for subsequent Neolithic expansions into the rest of Europe.

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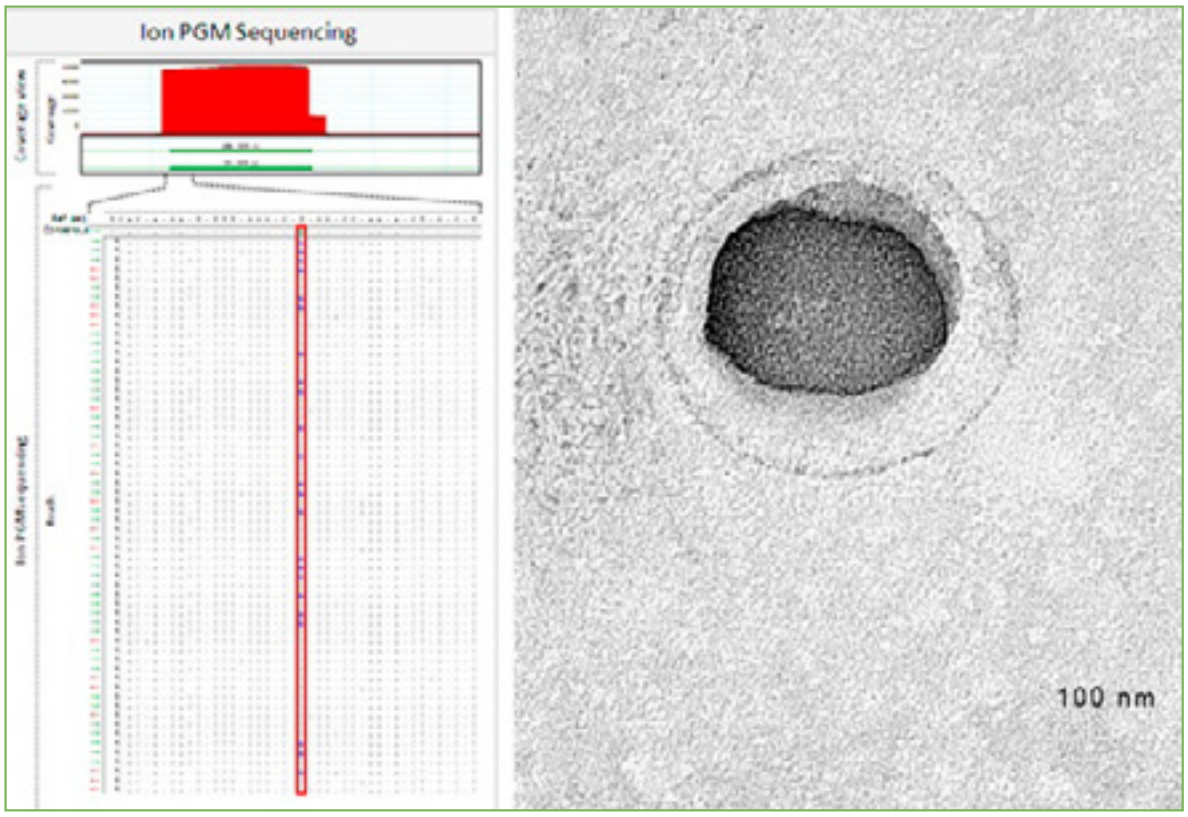
TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Bruno Cavadas	MSc	Portugal 2020 BI grant - Master	PhD student	100
Hugo Oliveira	BSc	Non-paid Student	Master student	100
Joana Ferreira	MSc	Norte 2020 BI grant - Master	PhD student	100
Joana Pereira	PhD	Contract (com termo)	Researcher	100
Luísa Pereira	PhD	Contract (sem termo)	Researcher	100
Marisa Oliveira	MSc	FCT PhD grant	PhD student	100
Nicole Pedro	MSc	FCT BI grant - Master	Research fellow	100
Patrícia Marques	PhD	FCT Post-doc grant	Post-doc	100
Susana Seixas	PhD	Contract (com termo)	Researcher	100
Verónica Fernandes	PhD	FCT Post-doc grant	Post-doc	100

GENETIC DYNAMICS OF CANCER CELLS

GROUP LEADER: **José Carlos Machado**



AIM OF THE GROUP

The scientific question that drives our research group is how genetic information is transmitted among the diverse cellular constituents of a tumor, and how that affects the heterogeneity and plasticity of cancer cells. We want to understand how mutant or aberrantly expressed molecules influence the interaction between cancer cells, and between cancer and non-cancer cells.

Objectives:

1. Identification of genetic causes of cancer and the validation of biomarkers with clinical relevance.
2. Identification and understanding of the dynamics of cancer-related genomic alterations in order to exploit and translate this knowledge for the clinical management of cancer patients.
3. Understand how neoplastic cell mutations trigger immune response and which mechanisms neoplastic cells use to escape immunosurveillance.
4. Understand how the flow of genetic and molecular information in cancer exosomes is involved in tumor progression, and if this communication could be a new therapeutic target for cancer treatment.
5. Identification of molecular factors involved in the interaction between stromal and cancer cells, and impact assessment of their inactivation on oncogenesis.

MAJOR ACHIEVEMENTS IN 2017

- We participated in the study that provided the guidelines for the use of next generation sequencing in molecular pathology of solid tumors in the laboratories that assist clinical services. These guidelines cover testing strategy, implementation in the clinics, sample requests, data analysis and reporting.
- We determined the presence of KRAS and TP53 mutations in circulating exosomes of healthy individuals and patients with pancreatic cancer and verified that KRAS mutations were detected in liquid biopsies of apparently healthy individuals although in a rare frequency. This indicates that the existence of KRAS mutations in liquid biopsies can be used as an indicator of cancer risk but the presence of clinical cancer cannot be assumed with certainty.
- We loaded exosomes derived from normal fibroblast-like mesenchymal cells with small interfering or short hairpin RNA molecules specific for oncogenic KrasG12D (iExosomes). In contrast to liposomes, the injection of iExosomes, into pancreatic cancer mouse models, subverts phagocytosis due to the CD47 protein, a "don't eat me" signal to monocytes. The preclinical data gathered in this study suggest that these vesicles are active therapeutic tools and have the potential to be used in the treatment of KrasG12D-positive pancreatic cancer patients.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Figueiredo, C, Camargo, MC, Leite, M, Fuentes-Panana, EM, Rabkin, CS and Machado, JC. Erratum to: Pathogenesis of Gastric Cancer: Genetics and Molecular Classification. Current topics in microbiology and immunology. 2017;400:E1 https://www.ncbi.nlm.nih.gov/pubmed/28608027 (Impact Factor: 5.829)
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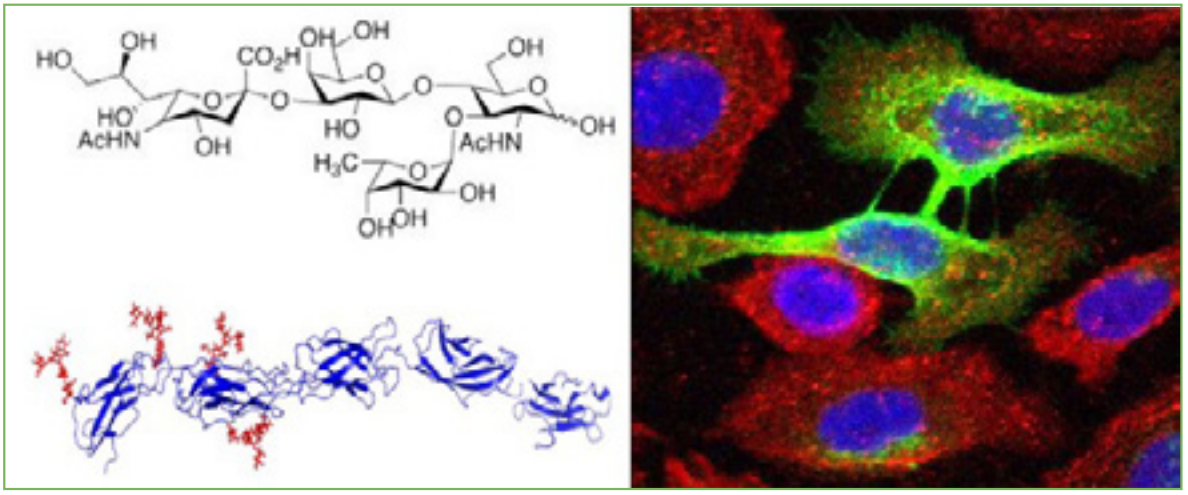
1. Cipriano, MA and Carneiro, F. O papel da biópsia nos tumores do fígado. In: A. Carvalho, G. Macedo and R.T. Marinho, editors. Carcinoma Hepatocelular. Uma década 2007-2017: Permanyer Portugal, 2017. p. 41-8

TEAM MEMBERS

Name	Academic degree	Professional situation
Alysia Wayenberg	Undergradute	Research Trainee
Ana Brandão	BSc	Master Student
Bárbara Adem	MSc	PhD Student
Carina Mesquita	BSc	Research Technician
Carlos Resende	PhD	Post Doc
Carolina Ruivo	MSc	PhD Student
Cecília Durães	PhD	Post Doc
Eugénio Gonçalves	Undergradute	Visiting Researcher
Fátima Carneiro	PhD	Researcher
Gabriela Fernandes	BSc	PhD Student
Gilza Gonçalves	BSc	Fellow
Helena Ferreira	MSc	PhD Student
Inês Batista	MSc	Fellow
Ivette Pacheco	PhD	Post Doc
Joana Marques	MSc	Fellow
Joana Martins	BSc	Master Student
Joana Reis	BSc	Fellow
João Pereira	MSc	Visiting Researcher
José Carlos Machado	PhD	Researcher
José Luis Costa	PhD	Assistant Researcher
Marina Baessa	Undergradute	Master Student
Marta Araújo	BSc	Master Student
Marta Pereira	BSc	Research Technician
Miguel Silva	MSc	GABBA PhD Student
Nuno Bastos	MSc	PhD Student
Nuno Rodrigues dos Santos	PhD	Researcher
Ricardo Pinto	BSc	PhD Student
Rita Barros	PhD	Consultant
Sara Andrade	PhD	Assistant Researcher
Sara Miranda	MSc	Fellow
Sofia Pereira	PhD	Post Doc
Sónia Melo	PhD	Researcher
Soraia Silva	MSc	Fellow
Susana Junqueira Neto	MSc	PhD Student
Tiago Vinhoza	PhD	Assistant Researcher
Venceslau Hespanhol	PhD	Researcher
Xiaogang Wen	MSc	Research Consultant

GLYCOBIOLOGY IN CANCER

GROUP LEADER: **Celso Reis**



AIM OF THE GROUP

The group "Glycobiology in Cancer" focus on the role that glycosylation plays in human cancer. The main goal of the group is the understanding of the role of glycosylation in carcinogenesis, tumour biology and cancer progression. We apply multidisciplinary approaches combining molecular and cell biology, (glyco) proteomics, animal models, and patients' cohorts of tumours for understanding the functions played by glycosylation in human cancer.
The main research objectives are:

- Evaluation of the role of glycans and glycan-binding proteins in cancer and pre-cancerous conditions addressing the molecular mechanisms controlling glycosylation of key proteins involved in cancer development and progression.
- Development of glycoengineered cell and animal models for understanding how glycosylation governs key mechanisms of epithelial cell biology and communication between cells, their interaction with immune cells and non-cellular components.
- Characterization of the molecular mechanisms underlying the glycan-mediated adhesion of Helicobacter pylori and other Helicobacter members and the understanding of the host-pathogen crosstalk in inflammation and carcinogenesis.
- Identification of novel glycan-based biomarkers for application in cancer diagnosis, prognosis and patient stratification.
- Development of novel glycan based therapeutic strategies for cancer.

MAJOR ACHIEVEMENTS IN 2017

- The characterization of the role of glycosylation in glycoproteins controlling cancer invasion and tumor progression, including the modulation of Tyrosine Kinase Receptors (TKRs) such as HER2, providing novel biomarkers with clinical applications. The findings on the glycosylation of HER2 in gastric cancer demonstrates the importance of taking into consideration this post-translational modification of the protein as a key factor defining the function of the TKRs in cancer. In addition, provides the basis for further investigation on the role that this glycosylation plays in gastric cancer targeted therapies and patients´ therapy response (Duarte et al., 2017).

- The understanding of the glycosyltransferases controlling the aberrant cell glycosylation in cancer; including the understanding the role of early O-glycosylation and core-fucosylation in cancer (Magalhães et al., 2017; Gomes et al., 2017).
- The characterization of Sialyl-Tn antigen as a biomarker that identifies muscle-invasive bladder cancer basal and luminal subtypes facing decreased survival, being expressed by circulating tumor cells and metastases (Lima et al., 2017).
- The development and extensive epitope mapping and characterization of a novel unique anti-Tn antibody detecting gastric cancer cells. This novel monoclonal antibody detects specifically and with high affinity the truncated glycoform of O-glycans which is expressed by cancer cells, particularly in gastric carcinoma (Persson et al., 2017).
- The development of novel solid-phase proximity ligation assay for the detection of post-translational modifications of proteins. This innovative assay provides the detection of specific glycoforms of glycoproteins expressed in cancer cells (Oliveira et al., 2017).

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

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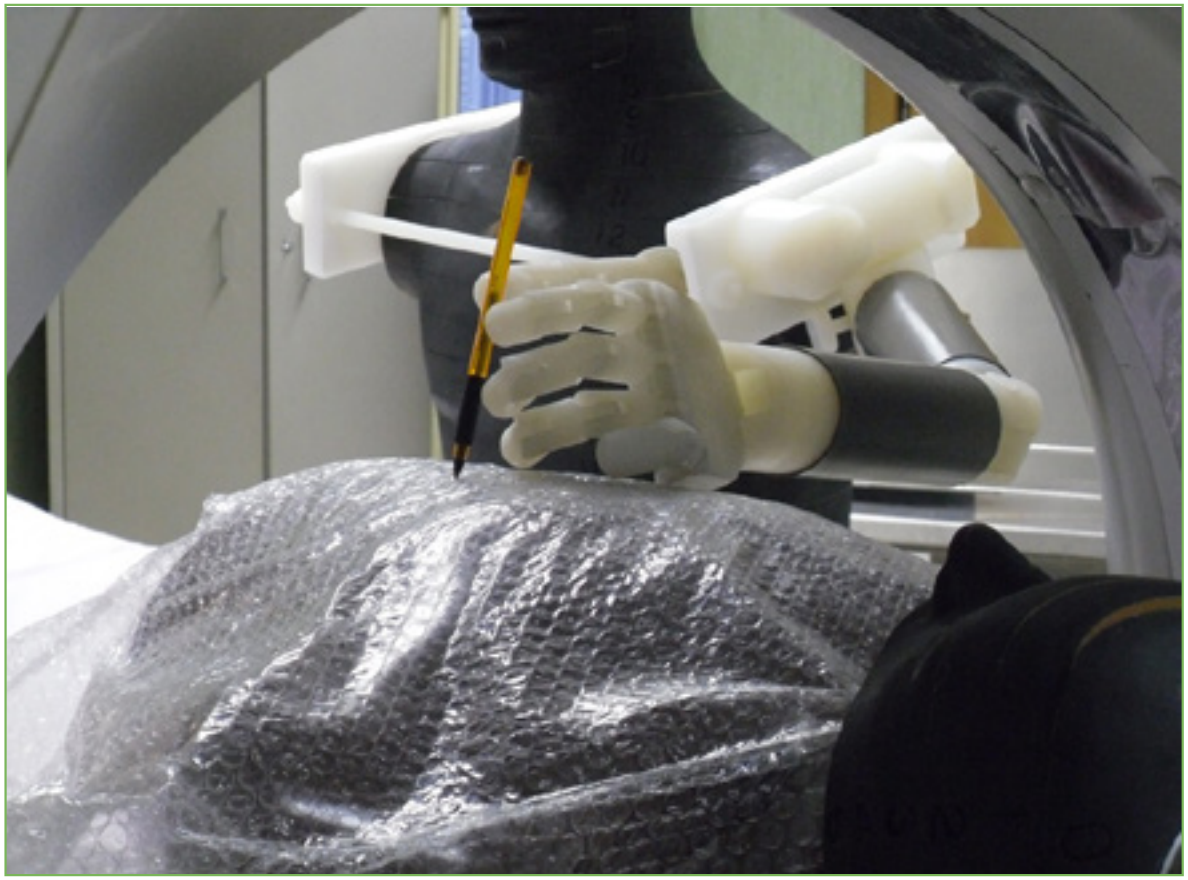
TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Álvaro Martins	BSc	Non-paid Student	MSc student	100
Ana Magalhães	PhD	Employed	Researcher	100
Catarina Gomes	PhD	Felowship	FCT pos-doc fellow	100
Celso Reis	PhD	Employed	Principal Investigator	100
Daniela Freitas	MSc	Felowship	FCT PhD fellow	100
Diana Campos	PhD	Felowship	FCT pos-doc fellow	100
Fátima Gartner	Aggregation	Employed	Full Professor	60
Filipe Pinto	PhD	Felowship	FCT pos-doc fellow	100
Francisca Diniz	MSc	Employed	FCT Fellowship	100
Henrique Duarte	MSc	Employed	FCT PhD fellow	100
Hugo Osório	PhD	Employed	Researcher	100
Irina Amorim	PhD	Employed	Affiliated Researcher	10
Joana Gomes	PhD	Employed	Lab Manager	100
Joana Rodrigues	MSc	Employed	Fellow	100
Juliana Calheiros	MSc	Employed	Fellow	100
Juliana Poças	MSc	Employed	Fellow	100
Luís Carlos Oliveira Lima	PhD	Employed	FCT pos-doc fellow	10
Mariana Ferreira	BSc	Non-paid Student	MSc student	100
Meritxell Balmaña	PhD	Employed	European Union Researcher	100
Rita Matos	MSc	Felowship	FCT PhD fellow	100
Stefan Mereiter	PhD	Felowship	FCT pos-doc fellow	100

MEDICAL PHYSICS, RADIOBIOLOGY AND RADIATION PROTECTION

GROUP LEADER: **João.A.M.Santos**



AIM OF THE GROUP

The Medical Physics, Radiobiology and Radiation Protection Group was formed in the beginning of 2008 housed by the IPO-Porto Research Center. Its members are mainly physicists and radiobiologists but also include other expertises such as radiopharmacy and clinical practitioners. It is the only Medical Physics and Radiobiology research group in Portugal whose activities are developed entirely in a hospital environment. The work of the group focuses on the application of the methodology of physics and radiobiology to solve specific problems related to health care, especially in the area of ionizing radiation, both from the perspective of the patient procedures optimization or in the perspective of the protection in the event of professional exposure to ionizing radiation. Being focused in the interaction of ionizing radiation and biological tissues, the question of radiation protection arises immediately. The group embraced already critical personal exposure due to highly heterogeneous radiation fields during the project “Dose distribution mapping and Monte Carlo simulations in CT-fluoroscopy” (PTDC/SAU-ENB/115792/2009) and patient exposure during intra-operatory radiotherapy during the project “IORT: the effect of shielding on dose distributions in intra-operative electron radiotherapy: a Monte Carlo simulations study.” (PTDC/SAU-ENB/117631/2010). Both these studies were complemented by Monte Carlo (MC) simulations. This methodology, with increasing computer power over

the last years, is becoming a benchmark method to simulate “difficult-to-execute-in-practice” procedures in ionizing radiation physics, where exposure of subjects must be very well justified. Over the year of 2017, the group extended this methodology to external radiotherapy using Penelope based PRIMO software, which has become one of the main strategic lines of research. Monte Carlo methods are being used also in the field of Nuclear Medicine, both for imaging and radiation spectrum analysis and optimization.

The group is involved in several national and international collaborations such as Faculdade de Ciências da Universidade do Porto, Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Instituto Superior Técnico (IST/CTN), INESC Porto, Universidade de Aveiro (Dep. Eng. Mecânica), Universidade de Coimbra (Centro de Informática e Sistemas da Universidade de Coimbra; LIP), Faculdade de Ciências da Universidade de Lisboa, Universidade do Minho (MEMS), Institute of Nuclear Physics PAN, Radzikowskiego 152, PL 31-342 Krakow, Radiation Chemistry and Dosimetry Laboratory, Bijenička c. 54, HR-10000 Zagreb, Croatia, Greek Atomic Energy Commission (EEAE), Dosimetry and Calibration Department P.O. Box 60092, 153 10 Agia Paraskevi, Athens, Greece, SCK•CEN | Belgian Nuclear Research Centre, Unit Research in Dosimetric Applications, Boeretang 200 - BE-2400 Mol, among others. The group has one Full Members (J.A.M. Santos) in the European Radiation Dosimetry Group (Eurados), and one Corresponding Member (J. Lencart), in the Workgroup 9, WG9 (Radiation Protection in Radiotherapy).

MAJOR ACHIEVEMENTS IN 2017

1. Monte Carlo volumetric arc therapy (VMAT) simulation

The advanced modalities of radiotherapy like the Volumetric Modulated Arc Therapy (VMAT) use non-uniform intensity fields allowing complex dose distribution patterns. The intensity modulation is obtained through the motion of the beam modifiers and, in concrete, in the case of the VMAT therapy through the synchronized motion between the Multileaf Collimator (MLC) motion and the Gantry rotation. The introduction of continuous motion with continuous treatment delivery introduces uncertainties and pose difficulties in the dose distribution calculation by Treatment Planning Systems (TPS). In order to deal with the uncertainties introduced a dedicated Quality Assurance (QA) program and patient-specific dose verifications are requested which besides capturing the staff to perform the QAs it also consumes a precious time that could be used in effective treatment. A viable alternative as a recognized golden standard for dose calculation given its most detailed description of radiation-matter interaction could be through the use of Monte Carlo (MC) methods. The caveats to this method are the not trivial set-up of the RT model and treatment and also the time needed for execute the calculation. These caveats have prevented the routinely use in clinic of this method, but recently, the PRIMO software was proposed, providing several built-in RT units models, including TrueBeam, and with a user interface that facilitates this work. Nevertheless, VMAT is not implemented yet and the core of this work is about the feasibility of using PRIMO for advanced dynamic MC simulations. With this purpose, a TrueBeam was simulated in PRIMO using 6 and 10MeV in Flatness Filter Free mode and at 15MeV with Flatness Filter. The results were validated by Gamma Function (2%, 2mm) based on reference measurements in water tank. Since PRIMO can deal with multiple static fields, following a Position Probability Sampling (PPS), the dynamic treatment delivery is divided into a customizable number of probabilistically sampled static configurations of jaws, leaves and gantry angles. In-house algorithms were developed to interpolate the LINAC geometrical information along the procedure once the planned information is retrieved from the DICOM plan file. A graphical user interface (GUI) was developed to assist non-expert users to configure PRIMO to simulate complex deliveries. Static simulations in reference conditions showed always > 97% of Gamma points < 1 for PDD and profiles at various depths and fields sizes for the 6, 10 and 15MeV primary beam respectively. The GUI properly read, manipulated and wrote the configuration data in a .ppj format, which was accepted by PRIMO. The MLC

model was validated against gafchromic measure for the 6 and 10 MeV energies in FFF mode. The GUI successfully automatized the needed tasks like the TPS treatment plan import, the dynamic treatment sampling, the primo file configuration, the several PRIMO output dose files integration and the export of the result in DICOM v format. Several tests were made to validate the sampling algorithm and the suggested workflow to implement the VMAT simulation with the aid of PRIMO. The results obtained from gamma comparisons gave reliable outcome and great expectations for future work.

2. Out-of-field Monte Carlo Dose evaluation

2.1 Influence of extrafocal dose in the out-of-field dose distribution

Since paediatric patients have higher life expectancy than adults and tend to receive higher secondary organ doses due to geometrical factors, secondary induced cancer due to out-of-field dose among paediatric patients is thus an increased concern. This work focusses on the influence of extrafocal dose in the out-of-field dose distribution using a paediatric anthropomorphic phantom. Monte Carlo simulations (Penelope) and Gafchromic EBT3 2D dose distribution measurement will be assessed.

A 5-year pediatric phantom (hypothetical brain lesion) was irradiated by Varian TrueBeam 120HD MLC linac, using four 6MV Flattening Filter Free (FFF) static fields. A cranio-caudal beam was employed. The plan was simulated by Monte-Carlo (MC) simulation using PRIMO software. The 2D dose distributions at several distances from the isocenter were measured using Gafcromic EBT3 films. The results were evaluated using 2D Gamma index on PTW-Verisoft software. MC simulations were previously validated by gamma index method (98% of points <1; 2mm, 2%).

Dose distributions were evaluated at 10, 15 and 17.5 cm away from the isocenter. The maximum local measured doses were 3.5, 1.6 and 1cGy per Gy at isocentre respectively. A well-defined rectangular shaped dose distribution was noticed in the films located at 15 and 17.5 cm from the isocentre. The same shape was also detected in all the MC simulations of the same planes. The rectangular shape was not observed in the TPS (Acuros nor AAA). The centre of this rectangular shape is aligned with the isocentre, and the width is consistent with the X-jaws opening direction. The dose values inside this rectangle are approximately 150% of the dose values in the surrounding regions.

The rectangular shaped dose distribution was linked to the extrafocal dose due to the cranio-caudal beam, which propagates significantly in the out-of-field regions (lungs, heart, etc.), even after applying known methodologies to lower it such as using FFF modes; choosing lower-energy beams; and limiting the Y-field size.

2.2. Dose Distributions in a Pediatric Phantom in External Radiotherapy

Patients undergoing radiotherapy are exposed to out-of- field scattered and leakage radiation, which may induce secondary cancer in long-term survivors. The induction of secondary cancer in pediatric patients is an increased concern, because they have increasingly higher life expectancy, and tend to receive higher secondary organ doses than adults due to geometrical factors. Radiation-induced thyroid and breast cancers have been observed in pediatrics after receiving doses as low as 100 mGy. While the dosimetric accuracy of treatment planning systems (TPS) is known to decrease in the out-of- field region, Monte Carlo (MC) is nowadays the most reliable method in dose calculation. A PENELOPE based MC code named PRIMO was tested for out-of- field dose estimation in pediatric irradiation. a 5-year pediatric anthropomorphic phantom was irradiated by Varian Triology linac, using three 6MV static fields beams for a brain tumor. The treatment plan was calculated in Varian Eclipse TPS, using Analytic Anisotropic Algorithm (AAA). The 2D dose distributions at thyroid and lung levels were measured using Gafcromic EBT3 films. The plan was simulated in PRIMO after

adjusting the primary beam parameters based on reference data in water phantom. PRIMO output data was reshaped, manipulated and re-written as DICOM files for comparisons with both measured and TPS calculated dose using 2D Gamma Function (3%, 3mm) on DoseLab Pro software. The maximum measured doses per 1 Gy at isocenter (0 cm) were 1.5 cGy and 8 mGy at thyroid (10.25 cm) and lung levels (15.25 cm) respectively. Comparing simulated and measured dose distribution one obtained 82.6% and 88.8% of gamma points <1 at thyroid and lung levels respectively. The difference between measured and TPS calculated dose distributions could easily be accessed visually. For secondary induced cancer risk estimation, the present TPS, even using a reliable algorithm as AAA, is not generally satisfactory for out-of- field dosimetry. Alternative tools, like MC simulations are necessary if correct dose estimation must be obtained for risk models application.

3. Development of computer tools of image analysis using advanced methods of neural networks: Work in Development

3.1. Evaluation of treatment response using "traditional" machine learning techniques using the extraction of characteristics in PET / CT volumes

Assessment of response to treatment is critical in a medical setting. Each patient has their individual and unique characteristics that make it impossible to predict correctly the final outcome of a treatment before its beginning. Therefore, it is necessary to evaluate and readjust the treatment during its course and taking into account the response that each specific patient over time.

In this line of research, we intend to extract automatically, and from PET / CT, markers that characterize the evolution of the treatment, a technique denominated in the radiometric literature. Thus, said labels (typically shape and texture descriptors) are automatically extracted from PET / CT volumes purchased prior to and after the first two treatment cycles. Since we are working with three-dimensional information, preference will be given to 3D marker extraction. These markers are used to train classification models that will later be used to classify new cases, thus assisting medical specialists in the decision to change or maintain current treatment.

3.2. Evaluation of treatment response using deep learning techniques in PET / CT volumes

As previously mentioned, a new group of techniques called "deep learning" has emerged in the literature that has surpassed all "traditional" techniques and even achieved comparable human performances. It is the objective of this line of work to apply automatic deep learning methods, in order to develop tools to aid in the evaluation of the response to treatment. These tools will be instrumental in reducing human error and making the process of evaluating response to treatment faster, thus enabling more effective treatment adjustment. The focus will be on the application of Convolutional Neural Networks (CNNs), because they have been shown to be the most suitable for classification of images (and volumes). The type of filters to be used in CNNs will be 3D so as not to lose the spatial information present in the PET / CT data. The architecture (number and size of filters, number of layers, etc.) will be adjusted throughout the work in order to better characterize the available information, consisting of PET / CT volumes acquired before and after some treatment cycles.

3.3. Automatic segmentation of regions of interest for radiology treatment in PET / CT

In order to plan a radiological treatment it is necessary to identify three regions, called GTV, CTV and PTV. GTV (gross tumor volume) represents the position and extent of the part of the tumor that is visible to the naked eye, palpable, or visible through imaging techniques. The CTV (clinical target volume) includes GTV and a margin where it is assumed that cancer is also present. This is typically the most difficult volume to delineate due to the lack of visual clues present in the current imaging methods. It is thus done based on the expert's experience. Finally, the PTV (planning target volume) is a geometric concept developed to ensure that the radiotherapeutic dose is effectively applied to the CTV and takes into account uncertainties in the planning

and transfer of treatment. All of the above volumes are usually outlined by those skilled in the art, which has the disadvantages of high intra and inter specialist variability, and other human factors such as errors due to fatigue, and also high costs. The aim of this line of work is to develop tools to assist the specialists in this time-consuming task, improving the quality and speed of this process, which will be transmitted in the possibility of performing earlier treatments with a smaller area of exposure, that is, more localized treatments , and consequently more effective with fewer side effects.

4. Scintillating fiber optic dosimeters for breast and prostate brachytherapy

As part of the "PRO-DOSE – Dispositivo para dosimetria in-vivo em braquiterapia", Projeto: 17816 : NU-RISE LDA (33/SI/2015) project, a fiber optical scintillation system for in-vivo measurements was developed and tested by yhe University of Aveiro, Nu-Rise and the GFMRPT group. Brachytherapy is a radiotherapy modality where the radioactive material is placed close to the tumor, being a common treatment for skin, breast, gynecological and prostate cancers. These treatments can be of low-dose rate, using isotopes with mean energy of 30 keV, or high-dose-rate, using isotopes such as 192Ir with a mean energy of 380 keV. Currently these treatments are performed in most cases without in-vivo dosimetry for quality control and quality assurance. We developed a dosimeter using small diameter probes that can be inserted into the patient's body using standard brachytherapy needles. By performing real-time dosimetry in breast and prostate brachytherapy it will be possible to perform real-time dose correction when deviations from the treatment plan are observed. The dosimeter presented in this work was evaluated in-vitro. The studies consisted in the characterization of the dosimeter with 500 m diameter sensitive probes (with a BCF-12 scintillating optical ber) using an inhouse made gelatin breast phantom with a volume of 566 cm3. A breast brachytherapy treatment was simulated considering a tumor volume of 27 cm3 and a prescribed absolute dose of 5 Gy. The dose distribution was determined by the Inverse Planning Simulated Annealing (IPSA) optimization algorithm (ELEKTA). The dwell times estimated from the experimental measurements are in agreement with the prescribed dwell times, with relative error below 3%. The measured signal-to-noise ratio (SNR) including the stem-effect contribution is below 3%.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Torras, MG, Fundowicz, M, Aliste, L, Asensio, E, Boladeras, AM, Borras, JM, Carvalho, L, Castro, C, Deantonio, L, Konstanty, E, Krengli, M, Kruszyna, M, Lencart, J, Macia, M, Marin, S, Munoz-Montplet, C, Pisani, C, Pinto, D, Puigdemont, M, Guedea, F, Aguiar, A, Milecki, P and Malicki, J. Improving radiation oncology through clinical audits: Introducing the IROCA project. Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology. 2017;22(5):408-14 http://www.ncbi.nlm.nih.gov/pubmed/28831281 (Impact Factor: NA)
2. Santos, MS, Soares, JP, Henriques Abreu, P, Araújo, H and Santos, J. Influence of Data Distribution in Missing Data Imputation. Artificial Intelligence in Medicine. 2017:285-94 https://link.springer.com/chapter/10.1007/978-3-319-59758-4_33 (Impact Factor: 2.879)
3. Simoes, H, Lopes, AL, Travassos, C, Crespo, P, Barros, MA, Lencart, J, Rachinhas, PJBM and Santos, JAM. Monitoring Tumor Lung Irradiation With Megavoltage Patient-Scattered Radiation: A Full System Simulation Study. IEEE Transactions on Radiation and Plasma Medical Sciences. 2017;1(5):452-9 https://ieeexplore.ieee.org/document/7971974/ (Impact Factor: NA)
4. Ghareeb, F, Silva, S., Lencart, J., Borges, F., Santos, J.A.M. Comparison of measured and calculated out-of-field doses in a paedriatic anthropomorphic phantom - out of the body scatter contribution evidence. Radiation and Applications (RAD Journal). 2017;2:20-5 http://www.rad-journal.org/paper.php?id=49 (Impact Factor: NA)
5. Moutinho, LM, Castro, IF, Freitas, H, Melo, J, Silva, P, Gonçalves, A, Peralta, L, Rachinhas, PJ, Simões, PCPS, Pinto, S, Pereira, A, Santos, JAM, Costa, M and Veloso, JFCA. Scintillating fiber optic dosimeters for breast and prostate brachytherapy. SPIE BiOS. 2017;10058:9 https://www.spiedigitallibrary.org/conference-proceedings-of-spie/10058/100580C/Scintillating-fiber-optic-dosimeters-for-breast-and-prostate-brachytherapy/10.1117/12.2254397.short?SSO=1 (Impact Factor: NA)

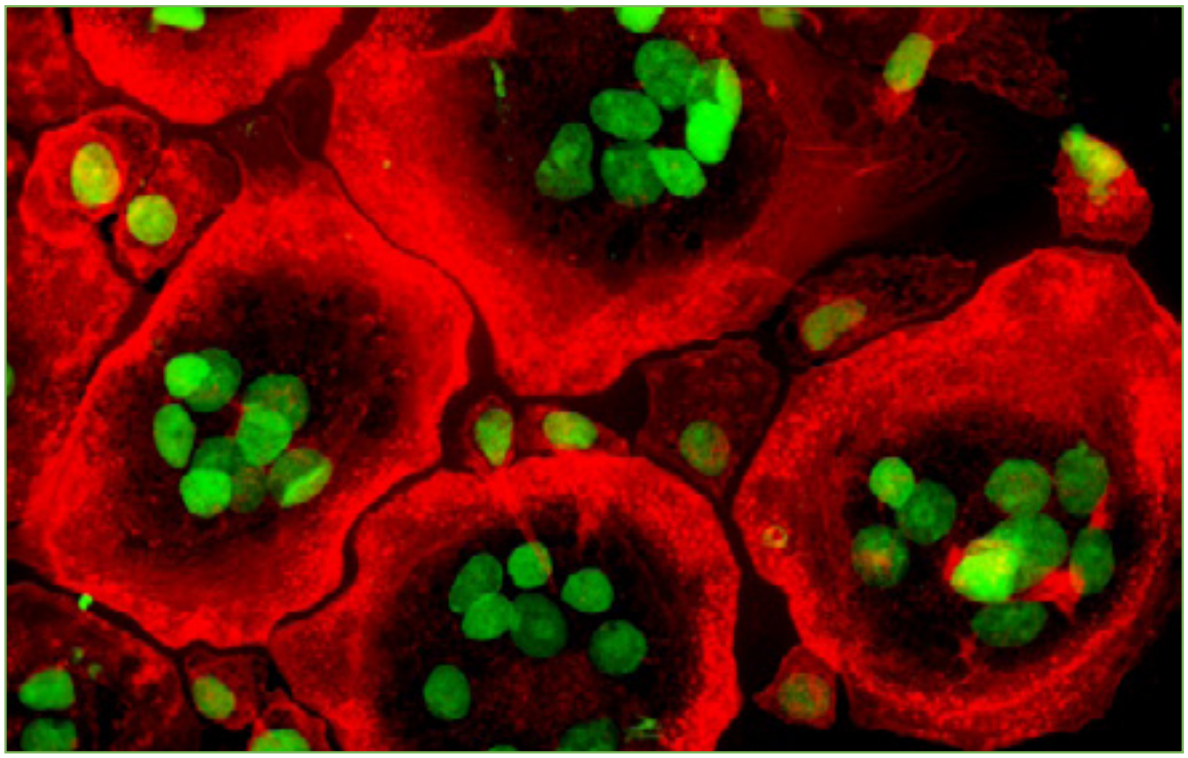
6. Nogueira, MA, Abreu, PH, Martins, P, Machado, P, Duarte, H and Santos, J. Image descriptors in radiology images: a systematic review. Artificial Intelligence Review. 2016;47(4):531-59 https://link.springer.com/article/10.1007%2Fs10462-016-9492-8 (Impact Factor: 3.814)
7. Nogueira, MA, Abreu, PH, Martins, P, Machado, P, Duarte, H and Santos, J. An artificial neural networks approach for assessment treatment response in oncological patients using PET/CT images. BMC medical imaging. 2017;17(1):13 http://www.ncbi.nlm.nih.gov/pubmed/28193201 (Impact Factor: 1.635)
8. Teles, P, Nikodemova, D, Bakhanova, E, Becker, F, Knezevic, Z, Pereira, MF and Sarmento, S. A Review of Radiation Protection Requirements and Dose Estimation for Staff and Patients in CT Fluoroscopy. Radiation protection dosimetry. 2017;174(4):518-34 http://www.ncbi.nlm.nih.gov/pubmed/27522054 (Impact Factor: 0.822)
9. Lopes, AL, Simões, H, Crespo, P, Barata, JAS, Lencart, J and Santos, JAM. Impact of tumor contrast in orthogonal ray imaging: A prostate irradiation study 2016 IEEE Nuclear Science Symposium, Medical Imaging Conference and Room-Temperature Semiconductor Detector Workshop. 2017(January, art. no. 8069392) https://ieeexplore.ieee.org/document/8069392/ (Impact Factor: NA)
10. Travassos, C, Simoes, H, Crespo, P, Barros, MA, Lencart, J, Rachinhas, PJBM and Santos, JAM. Experimental characterization of megavoltage beams for orthogonal ray imaging 2016 IEEE Nuclear Science Symposium, Medical Imaging Conference and Room-Temperature Semiconductor Detector Workshop. 2017(2017-January, art. no. 8069472.) https://ieeexplore.ieee.org/document/8069472/ (Impact Factor: NA)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Alexandre Baptista Mendes Pereira	BSc	Employed	Medical Physics Expert	20
Ana Catarina Santos Souto	BSc	Employed	Medical Physics Expert	20
Anabela Gregório Dias	PhD	Employed	Medical Physicist	30
Bruno Miguel Ferreira Mendes	MSc	Employed	Medical Physicist	20
Carla Isabel Vaz Tavares Figueiredo Capelo	BSc	Employed	Radiopharmacist	20
Diana Jorge Pimparel Alves Nuno Pinto	BSc	Employed	Medical Physicist	20
Filipe Augusto Madeira Dias	MSc	Employed	Medical Physicist	20
Firas Ghareeb	MSc	Scholarship	PhD student	100
Inês Campos Monteiro Sabino Domingue	PhD	Scholarship	Post-doc	100
Inês Magalhães da Silva de Lucena e Sampaio	BSc	Employed	Physician (Nuclear Medicine)	20
Isabel Maria Guedes Bravo	PhD	Employed	Radiobiologist	50
Joana Borges Lencart e Silva	BSc	Employed	Medical Physics Expert	20
Joana Safira Neves dos Santos	MSc	Scholarship	Researcher	100
João António Miranda dos Santos	PhD	Employed	Medical Physics Expert	30
Jorge Eduardo Nunes Oliveira	MSc	Scholarship	Medical Physicist	100
José Pedto Amorim	MSc	Scholarship	PhD student	100
Luís Paulo Teixeira Cunha	MSc	Employed	Medical Physicist	20
Miriam Raquel Seoane Pereira Seguro Santos	MSc	Scholarship	PhD student	50
Ricardo José Pires Magalhães	BSc	Not employed	MSc student	100
Rogéria Maria Craveiro Pereira	MSc	Employed	Radiobiologist	50
Sara Patrícia de Almeida Pinto	MSc	Employed	Medical Physicist	20
Sofia Isabel de Castro e Silva	PhD	Employed	Medical Physicist	30
Vera Catarina Marques Antunes	MSc	Employed	Medical Physicist	20

MICROENVIRONMENTS FOR NEW THERAPIES

GROUP LEADER: **Mário Barbosa**



AIM OF THE GROUP

The MiNT Group bioengineers microenvironments to promote tissue regeneration/functional restoration through modulation of the host response. Pivotal in this strategy is the concept that biodegradable biomaterials can drive inflammation towards either pro- or anti-inflammatory microenvironments. This rational has been consistently followed since 2012, when we first demonstrated that a natural polysaccharide (chitosan) drives anti-inflammatory macrophage polarization. We have implemented the above strategy to bone injury and intervertebral disc degeneration, focusing on the spine. In collaboration with the Tumor Microenvironment Group we have applied the same strategy to colorectal cancer.

Our main goal is the development of biomaterials to modulate inflammation in the context of osteoarticular applications, namely in the spine, and in cancer therapies.

MAJOR ACHIEVEMENTS IN 2017

- As part of sustained strategy of the group to explore the properties and mechanisms of action of the pro-inflammatory molecule fibrinogen (Fg) we found that Fg stimulates TLR-4 on monocytes and induces BMP-2 expression (Oliveira MI, Acta Biomaterialia, 2017).
- Demonstration of the pro-inflammatory effect of Ch/γ-PGA nanoparticles as immunomodulatory therapy for antigen-presenting cells reprogramming, providing a new tool for anticancer therapies (Castro F et al., Acta Biomater, 2017).

- Evidence that human decellularized tissues, either healthy or cancer-derived, retain their native characteristics responsible for governing cell differentiation and that cancer-derived tissues polarize macrophages towards an anti-inflammatory phenotype (Pinto ML et al. Biomaterials, 2017).
- Demonstration of the tumor-suppressor miR-195 as an inhibitor of M1-macrophage polarization through reduction of TLR2 inflammatory pathway mediators (Bras et al., PlosOne, 2017).
- miR-25-3p and miR-15a-5p decrease proliferation, motility, invasiveness and angiogenic potential and increased apoptosis of ovarian cancer cells when combined with docetaxel (Rodriguez-Aguayo C et al., Cell Discovery, 2017).

The findings 2 and 3 result from a close collaboration with the Tumor Microenvironment Group.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Castro, F, Pinto, ML, Silva, AM, Pereira, CL, Teixeira, GQ, Gomez-Lazaro, M, Santos, SG, Barbosa, MA, Goncalves, RM and Oliveira, MJ. Pro-inflammatory chitosan/poly(gamma-glutamic acid) nanoparticles modulate human antigen-presenting cells phenotype and revert their pro-invasive capacity. Acta Biomater. 2017;63:96-109 https://www.ncbi.nlm.nih.gov/pubmed/28919508 (Impact Factor: 6.383)
2. Pinto, ML, Rios, E, Silva, AC, Neves, SC, Caires, HR, Pinto, AT, Duraes, C, Carvalho, FA, Cardoso, AP, Santos, NC, Barrias, CC, Nascimento, DS, Pinto-do, OP, Barbosa, MA, Carneiro, F and Oliveira, MJ. Decellularized human colorectal cancer matrices polarize macrophages towards an anti-inflammatory phenotype promoting cancer cell invasion via CCL18. Biomaterials. 2017;124:211-24 https://www.ncbi.nlm.nih.gov/pubmed/28209528 (Impact Factor: 8.806)
3. Bras, JP, Silva, AM, Calin, GA, Barbosa, MA, Santos, SG and Almeida, MI. miR-195 inhibits macrophages pro-inflammatory profile and impacts the crosstalk with smooth muscle cells. PloS one. 2017;12(11):e0188530 https://www.ncbi.nlm.nih.gov/pubmed/29166412 (Impact Factor: 2.766)
4. Rodriguez-Aguayo, C, Monroig, PDC, Redis, RS, Bayraktar, E, Almeida, MI, Ivan, C, Fuentes-Mattei, E, Rashed, MH, Chavez-Reyes, A, Ozpolat, B, Mitra, R, Sood, AK, Calin, GA and Lopez-Berestein, G. Regulation of hnRNPA1 by microRNAs controls the miR-18a-K-RAS axis in chemotherapy-resistant ovarian cancer. Cell discovery. 2017;3:17029 https://www.ncbi.nlm.nih.gov/pubmed/28904816 (Impact Factor: 4.462)
5. Silva, AM, Almeida, MI, Teixeira, JH, Maia, AF, Calin, GA, Barbosa, MA and Santos, SG. Dendritic Cell-derived Extracellular Vesicles mediate Mesenchymal Stem/Stromal Cell recruitment. Scientific reports. 2017;7(1):1667 https://www.ncbi.nlm.nih.gov/pubmed/28490808 (Impact Factor: 4.122)
6. Silva, AM, Teixeira, JH, Almeida, MI, Goncalves, RM, Barbosa, MA and Santos, SG. Extracellular Vesicles: Immunomodulatory messengers in the context of tissue repair/regeneration. Eur J Pharm Sci. 2017;98:86-95 https://www.ncbi.nlm.nih.gov/pubmed/27644894 (Impact Factor: 3.466)
7. Henriques Lourenco, A, Neves, N, Ribeiro-Machado, C, Sousa, SR, Lamghari, M, Barrias, CC, Trigo Cabral, A, Barbosa, MA and Ribeiro, CC. Injectable hybrid system for strontium local delivery promotes bone regeneration in a rat critical-sized defect model. Scientific reports. 2017;7(1):5098 https://www.ncbi.nlm.nih.gov/pubmed/28698571 (Impact Factor: 4.122)
8. Neves, N, Linhares, D, Costa, G, Ribeiro, CC and Barbosa, MA. In vivo and clinical application of strontium-enriched biomaterials for bone regeneration: A systematic review. Bone & joint research. 2017;6(6):366-75 https://www.ncbi.nlm.nih.gov/pubmed/28600382 (Impact Factor: 2.362)
9. Blazquez-Prunera, A, Almeida, CR and Barbosa, MA. Human Bone Marrow Mesenchymal Stem/Stromal Cells Preserve Their Immunomodulatory and Chemotactic Properties When Expanded in a Human Plasma Derived Xeno-Free Medium. Stem cells international. 2017;2017:2185351 https://www.ncbi.nlm.nih.gov/pubmed/28588620 (Impact Factor: 3.989)
10. Cunha, C, Almeida, CR, Almeida, MI, Silva, AM, Molinos, M, Lamas, S, Pereira, CL, Teixeira, GQ, Monteiro, AT, Santos, SG, Goncalves, RM and Barbosa, MA. Systemic Delivery of Bone Marrow Mesenchymal Stem Cells for In Situ Intervertebral Disc Regeneration. Stem cells translational medicine. 2017;6(3):1029-39 https://www.ncbi.nlm.nih.gov/pubmed/28297581 (Impact Factor: 4.929)
11. Antunes, JC, Pereira, CL, Teixeira, GQ, Silva, RV, Caldeira, J, Grad, S, Goncalves, RM and Barbosa, MA. Poly(gamma-glutamic acid) and poly(gamma-glutamic acid)-based nanocomplexes enhance type II collagen production in intervertebral disc. Journal of materials science. Materials in medicine. 2017;28(1):6 https://www.ncbi.nlm.nih.gov/pubmed/27885573 (Impact Factor: 2.448)

12. Oliveira, MI, Pinto, ML, Goncalves, RM, Martins, MCL, Santos, SG and Barbosa, MA. Adsorbed Fibrinogen stimulates TLR-4 on monocytes and induces BMP-2 expression. Acta Biomater. 2017;49:296-305 https://www.ncbi.nlm.nih.gov/pubmed/27856281 (Impact Factor: 6.383)
13. Chang, H, Zhang, H, Hu, M, Chen, JY, Li, BC, Ren, KF, Martins, MC, Barbosa, MA and Ji, J. Stiffness of polyelectrolyte multilayer film influences endothelial function of endothelial cell monolayer. Colloids Surf B Biointerfaces. 2017;149:379-87 https://www.ncbi.nlm.nih.gov/pubmed/27855357 (Impact Factor: 3.997)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position		Time %
Alexandre Pedro Tavares da Fonseca Magalhães	PhD	Researchers	Others	Education Ministry	20
Ana Catarina Leite Pereira	PhD	Researchers	Post-Doc Researcher	INEB	20
Ana Filipa Henriques Ferreira Lourenço	MSc	Students	PhD student	FCT	30
Andreia Machado da Silva	MSc	Students	PhD student	INEB	20
Carla Maria Teixeira de Oliveira	PhD	Academia	Assistant Professor	IPP	20
Carla Marisa dos Santos Cunha	PhD	Researchers	Post-Doc Researcher	FCT	20
Daniela Fernanda Pereira de Vasconcelos	MSc	Students	PhD student	FCT	20
Joana Caldeira Fernandes Frey Ramos	PhD	Researchers	Post-Doc Researcher	FCT	100
Joana Rita Cardoso Brandão e Pinto Ferreira	BSc	Students	PhD student	FEUP	100
João Paulo Heitor Brás	BSc	Students	PhD student	FEUP	20
José Henrique Carvalho Teixeira	MSc	Students	PhD student	INEB	50
Mafalda Bessa Martins Gonçalves	MSc	Students	PhD student	ICBAS/FCT	20
Maria Cabral Maio Molinos	MSc	Students	PhD student	ICBAS	100
Maria Cristina de Castro Ribeiro	PhD	Academia	Adjunct Professor	ISEP	30
Maria de Fátima Rodrigues Pereira de Pina	PhD	Academia	Associate Professor	FIOCRUZ	100
Maria Inês da Cunha Doutel de Almeida	PhD	Researchers	Post-Doc Researcher	FCT	100
Maria Judite Tavares Moreira Novais Barbosa	PhD	Academia	Assistant Professor	ICBAS - UP	20
Mário Adolfo Monteiro Rocha Barbosa	PhD	Academia	Full Professor	ICBAS	50
Nuno Silva de Morais Neves	PhD, MD	Researchers	Others	CHSJ	100
Raquel Madeira Gonçalves	PhD	Researchers	Assistant Researcher	INEB	50
Sandra Maria Ferreira Alves	PhD	Academia	Adjunct Professor	IPP	20
Susana Gomes dos Santos Barber	PhD	Researchers	Assistant Researcher	INEB	30

MOLECULAR ONCOLOGY AND VIRAL PATHOLOGY

GROUP LEADER: **Rui M. Medeiros**

AIM OF THE GROUP

The Molecular Oncology & Viral Pathology Group was established in 2002 and is currently coordinated by Rui Medeiros, PharmD, PhD.

The group research aims are especially focused on Pharmacogenomics and Molecular Epidemiology, including the role of tumor viruses on cancer development and treatment. The fundamental objective of the group is the molecular characterization of the mechanisms associated with the onset of cancer and its response to cancer therapy, particularly through the identification of biomarkers for cancer development and therapeutic outcome.

The research on Pharmacogenomics and Comparative Personalized Medicine is incorporated in individualized medicine that focuses on how biomolecular factors may influence individual responses to different medications affecting drug efficacy, drug side effects, and adverse events related to drug therapy.

The long-term goal of the research being conducted is identifying responders and non responders to medications and thus avoid adverse events and optimize drug dose. Our research activities are aimed to define clinically useful tools to improve clinical outcomes as a result of the right medicine tailored specifically for that patient. The ultimate outcome of our research will be the development of rational drug treatment algorithms based on a patient's genotype linking to other predictive biomarkers, demographics, disease state, as well as other coadministered drugs. The group also develops projects in the field of tumor virology, studying the association of viral pathogenesis (especially Human Papillomavirus and Epstein-Barr Virus) with carcinogenesis. Furthermore, the influence of virus on tumor behavior is under evaluation for Comparative Personalized Medicine.

MAJOR ACHIEVEMENTS IN 2017

During 2017, we published 27 manuscripts and the sum of the impact factors of the journals where it published was 77. Regarding the 5 most relevant publications of the group, the top 5 average score of the impact factor is 6.1 ranging from journal like Cancer treatment reviews (Impact factor: 8.589), through Cancer Lett (Impact factor: 6.375) to Oncotarget (Impact factor: 5.168). Since the beginning, the Molecular Oncology and Viral Pathology Group contributed to the training of young researchers in the several steps of academic activity (Bachelor, Master, Doctoral and Postdoctoral). During its running period the group Doctorate 20 PhD students (6 MD/clinicians and 14 Biomedical researchers) and contribute to the academic training of MSc (>50) and BSc students (>50). The scientific output of Molecular Oncology and Viral Pathology Group includes a total of 267 international peer reviewed publications.

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

1. Assis, J, Pereira, C, Nogueira, A, Pereira, D, Carreira, R and Medeiros, R. Genetic variants as ovarian cancer first-line treatment hallmarks: A systematic review and meta-analysis. Cancer Treat Rev. 2017;61:35-52 http://www.ncbi.nlm.nih.gov/pubmed/29100168 (Impact Factor: 8.122)
2. Ribeiro, J, Malta, M, Galaghar, A, Silva, F, Afonso, LP, Medeiros, R and Sousa, H. P53 deregulation in Epstein-Barr virus-associated gastric cancer. Cancer letters. 2017;404:37-43 http://www.ncbi.nlm.nih.gov/pubmed/28729047 (Impact Factor: 6.491)
3. Dias, F, Teixeira, AL, Ferreira, M, Adem, B, Bastos, N, Vieira, J, Fernandes, M, Sequeira, MI, Mauricio, J, Lobo, F, Morais, A, Oliveira, J, Kok, K and Medeiros, R. Plasmatic miR-210, miR-221 and miR-1233 profile: potential liquid biopsies candidates for renal cell carcinoma. Oncotarget. 2017;8(61):103315-26 https://www.ncbi.nlm.nih.gov/pubmed/29262564 (Impact Factor: NA)
4. Coelho, AL, Gomes, MP, Catarino, RJ, Rolfo, C, Lopes, AM, Medeiros, RM and Araujo, AM. Angiogenesis in NSCLC: is vessel co-option the trunk that sustains the branches? Oncotarget. 2017;8(24):39795-804 http://www.ncbi.nlm.nih.gov/pubmed/26950275 (Impact Factor: NA)
5. Santos, MD, Silva, C, Rocha, A, Nogueira, C, Castro-Pocas, F, Araujo, A, Matos, E, Pereira, C, Medeiros, R and Lopes, C. Predictive clinical model of tumor response after chemoradiation in rectal cancer. Oncotarget. 2017;8(35):58133-51 http://www.ncbi.nlm.nih.gov/pubmed/28938543 (Impact Factor: NA)
6. Morais, M, Dias, F, Teixeira, AL and Medeiros, R. MicroRNAs and altered metabolism of clear cell renal cell carcinoma: Potential role as aerobic glycolysis biomarkers. Biochimica et biophysica acta. 2017;1861(9):2175-85 http://www.ncbi.nlm.nih.gov/pubmed/28579513 (Impact Factor: 3.679)
7. Campos, AB, Ribeiro, J, Pinho Vaz, C, Campilho, F, Branca, R, Campos, A, Jr., Baldaque, I, Medeiros, R, Boutolleau, D and Sousa, H. Genotypic resistance of cytomegalovirus to antivirals in hematopoietic stem cell transplant recipients from Portugal: A retrospective study. Antiviral research. 2017;138:86-92 http://www.ncbi.nlm.nih.gov/pubmed/27887982 (Impact Factor: 4.307)
8. Ferreira, M, Teixeira, A, Mauricio, J, Lobo, F, Morais, A and Medeiros, R. Hypoxia and renal cell carcinoma: The influence of HIF1A+1772C/T functional genetic polymorphism on prognosis. Urologic oncology. 2017;35(8):532 e25- e30 http://www.ncbi.nlm.nih.gov/pubmed/28476527 (Impact Factor: 3.397)
9. Gil da Costa, RM, Peleteiro, MC, Pires, MA and DiMaio, D. An Update on Canine, Feline and Bovine Papillomaviruses. Transbound Emerg Dis. 2017;64(5):1371-9 http://www.ncbi.nlm.nih.gov/pubmed/27615361 (Impact Factor: 3.504)
10. Ribeiro, J, Oliveira, A, Malta, M, Oliveira, C, Silva, F, Galaghar, A, Afonso, LP, Neves, MC, Medeiros, R, Pimentel-Nunes, P and Sousa, H. Clinical and pathological characterization of Epstein-Barr virus-associated gastric carcinomas in Portugal. World journal of gastroenterology : WJG. 2017;23(40):7292-302 http://www.ncbi.nlm.nih.gov/pubmed/29142476 (Impact Factor: 3.300)
11. Gil da Costa, RM, Aragao, S, Moutinho, M, Alvarado, A, Carmo, D, Casaca, F, Silva, S, Ribeiro, J, Sousa, H, Ferreira, R, Nogueira-Ferreira, R, Pires, MJ, Colaco, B, Medeiros, R, Venancio, C, Oliveira, MM, Bastos, MM, Lopes, C and Oliveira, PA. HPV16 induces a wasting syndrome in transgenic mice: Amelioration by dietary polyphenols via NF-kappaB inhibition. Life Sci. 2017;169:11-9 http://www.ncbi.nlm.nih.gov/pubmed/27888116 (Impact Factor: 3.234)

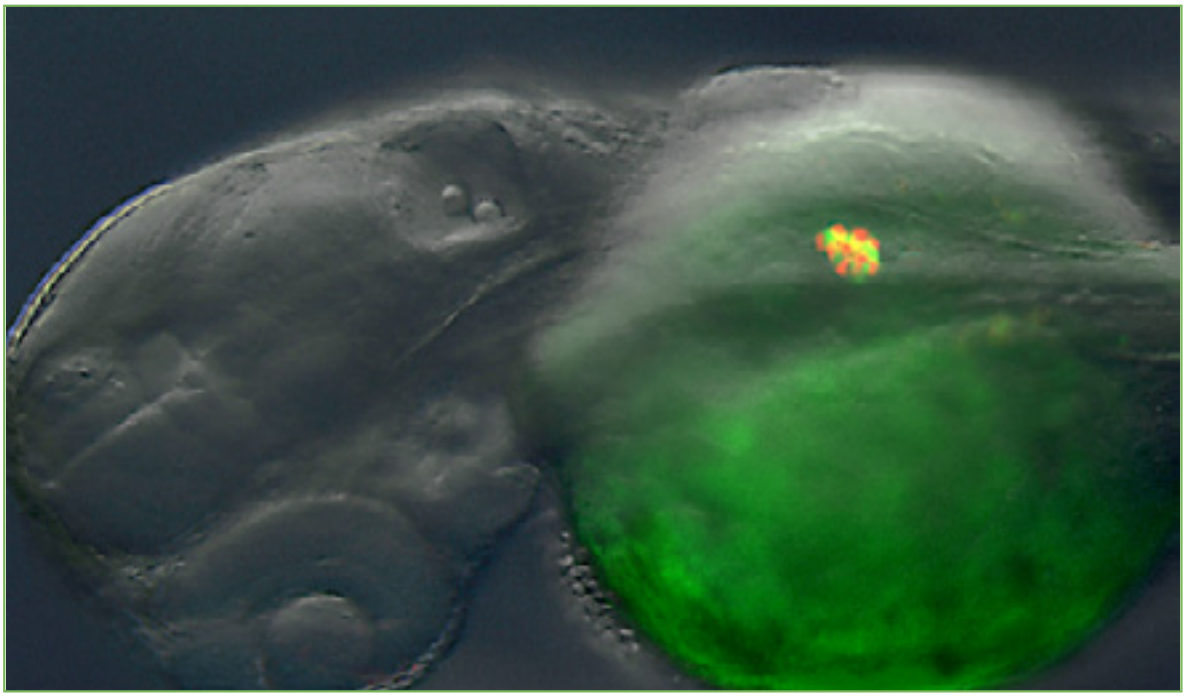
12. Santos, JMO, Fernandes, M, Araujo, R, Sousa, H, Ribeiro, J, Bastos, M, Oliveira, PA, Carmo, D, Casaca, F, Silva, S, Teixeira, AL, Gil da Costa, RM and Medeiros, R. Dysregulated expression of microRNA-150 in human papillomavirus-induced lesions of K14-HPV16 transgenic mice. Life Sci. 2017;175:31-6 http://www.ncbi.nlm.nih.gov/pubmed/28302562 (Impact Factor: 3.234)
13. Santos, C, Vilanova, M, Medeiros, R and Gil da Costa, RM. HPV-transgenic mouse models: Tools for studying the cancer-associated immune response. Virus research. 2017;235:49-57 http://www.ncbi.nlm.nih.gov/pubmed/28385491 (Impact Factor: 2.484)
14. Pinto, R, Assis, J, Nogueira, A, Pereira, C, Pereira, D and Medeiros, R. Rethinking ovarian cancer genomics: where genome-wide association studies stand? Pharmacogenomics. 2017;18(17):1611-25 http://www.ncbi.nlm.nih.gov/pubmed/29095100 (Impact Factor: 2.302)
15. Ribeiro, J, Oliveira, C, Malta, M and Sousa, H. Epstein-Barr virus gene expression and latency pattern in gastric carcinomas: a systematic review. Future Oncol. 2017;13(6):567-79 http://www.ncbi.nlm.nih.gov/pubmed/28118740 (Impact Factor: 2.369)
16. Nogueira, A, Assis, J, Faustino, I, Pereira, D, Catarino, R and Medeiros, R. Base excision repair pathway: PARP1 genotypes as modulators of therapy response in cervical cancer patients. Biomarkers. 2017;22(1):70-6 http://www.ncbi.nlm.nih.gov/pubmed/27323894 (Impact Factor: 1.976)
17. Neves, M, Marinho-Dias, J, Ribeiro, J and Sousa, H. Epstein-Barr virus strains and variations: Geographic or disease-specific variants? Journal of medical virology. 2017;89(3):373-87 http://www.ncbi.nlm.nih.gov/pubmed/27430663 (Impact Factor: 1.988)
18. Da Costa, RMG, Araujo, R, Santos, JMO, Fernandes, M, Neto, T, Sousa, H, Ribeiro, J, Bastos, M, Oliveira, PA, Carmo, D, Casaca, F, Silva, S, Lopes, C and Medeiros, R. Regulation of miRNA-146a and miRNA-150 Levels by Celecoxib in Premalignant Lesions of K14-HPV16 Mice. Anticancer Res. 2017;37(6):2913-8 http://www.ncbi.nlm.nih.gov/pubmed/28551628 (Impact Factor: 1.865)
19. Santos, MD, Silva, C, Rocha, A, Nogueira, C, Castro-Pocas, F, Araujo, A, Matos, E, Pereira, C, Medeiros, R and Lopes, C. Prognostic and Therapeutic Potential Implications of Genetic Variability in Prostaglandin E2 Pathway Genes in Rectal Cancer. Anticancer Res. 2017;37(1):281-91 http://www.ncbi.nlm.nih.gov/pubmed/28011504 (Impact Factor: 1.865)
20. Alvarado, A, Gil da Costa, RM, Faustino-Rocha, AI, Ferreira, R, Lopes, C, Oliveira, PA and Colaco, B. Effects of exercise training on breast cancer metastasis in a rat model. International journal of experimental pathology. 2017;98(1):40-6 http://www.ncbi.nlm.nih.gov/pubmed/28556395 (Impact Factor: 1.938)
21. Fraga, A, Ribeiro, R, Coelho, A, Vizcaino, JR, Coutinho, H, Lopes, JM, Principe, P, Lobato, C, Lopes, C and Medeiros, R. Genetic polymorphisms in key hypoxia-regulated downstream molecules and phenotypic correlation in prostate cancer. BMC urology. 2017;17(1):12 https://www.ncbi.nlm.nih.gov/pubmed/28143503 (Impact Factor: 1.792)
22. Carvalho, S, Santos, M, Lima, L, Mota-Pereira, J, Pimentel, P, Maia, D, Correia, D, Gomes, S, Cruz, A and Medeiros, R. IL6-174G > C genetic polymorphism influences antidepressant treatment outcome. Nordic journal of psychiatry. 2017;71(2):158-62 https://www.ncbi.nlm.nih.gov/pubmed/27796193 (Impact Factor: 1.764)
23. Silva, J, Cerqueira, F and Medeiros, R. Acceptability of self-sampling in Portuguese women: the good, the bad or the ugly? Sexual health. 2017;14(3):298-300 http://www.ncbi.nlm.nih.gov/pubmed/28063461 (Impact Factor: 1.246)
24. Chambuso, RS, Shadrack, S, Lidenge, SJ, Mwakibete, N and Medeiros, RM. Influence of HIV/AIDS on Cervical Cancer: A Retrospective Study From Tanzania. Journal of global oncology. 2017;3(1):72-8 http://www.ncbi.nlm.nih.gov/pubmed/28717744 (Impact Factor: NA)
25. Dinis, V, Bento, AM, Teixeira, AL, Gouveia, N, Bogas, V, Porto, MJ and Corte-Real, F. Comparative study between a direct DNA quantification methodology and the standardized methodology in the forensic workflow. Forensic Science International: Genetics Supplement Series. 2017;6:e216-e7 http://www.sciencedirect.com/science/article/pii/S187517681730238X (Impact Factor: 5.637)
26. Pontes, L, Sousa, JC and Medeiros, R. SNPs and STRs in forensic medicine. A strategy for kinship evaluation. Archiwum medycyny sadowej i kryminologii. 2017;67(3):226-40 http://www.ncbi.nlm.nih.gov/pubmed/29460612 (Impact Factor: NA)
27. Espirito Santo, A, Chacim, S, Ferreira, I, Leite, L, Moreira, C, Pereira, D, Dantas, M, Nunes, M, Viterbo, L, Moreira, I, Martins, A, Oliveira, I, Domingues, N, Mariz, J and Medeiros, R. Southwestern Oncology Group pretreatment risk criteria as predictive or prognostic factors in acute myeloid leukemia. Mol Clin Oncol. 2017;6(3):384-8 http://www.ncbi.nlm.nih.gov/pubmed/28451418 (Impact Factor: 1.500)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Luísa Pereira Teixeira	PhD	Scholarship FCT	Postdoc	100
Ana Luísa Pequeno Coelho	PhD	Scholarship LPCC	Postdoc	70
Ana Carina Martins Pereira	PhD	Scholarship FCT	Postdoc	40
Augusto José André Nogueira	MSc	Scholarship FCT	PhD Student	100
Áurea Rosa Nunes Pereira Lima	PhD	Employed HVR	MD	30
Francisca Guilherme Carvalho Dias	MSc	Scholarship ESTIMA	PhD Student	100
Hugo Manuel Lopes de Sousa	PhD	Employed IPO-Porto	MD/TSS	30
Joana Isabel Gomes Assis	MSc	Scholarship FCT	PhD Student	100
Joana Maria de Oliveira Santos	MSc	Scholarship LPCC	PhD Student	100
Joana Patrícia Costa Ribeiro	MSc	Scholarship FCT	PhD Student	100
Joana Sousa Gonçalves de Marinho Dias	MSc	Employed IPO-Porto	PhD Student	100
Mara Sofia Aires Fernandes	MSc	Scholarship LPCC	PhD Student	100
Mariana Gomes Morais	MSc	Scholarship LPCC	PhD Student	100
Maria Natalia Rios Vieira da Costa	PhD	Scholarship ESTIMA	Postdoc	100
Marlene Elisabete Moreira dos Santos	PhD	Employed Politec.Inst.	Aux. Professor	40
Mónica Patrícia Silva Gomes	MSc	Scholarship LPCC	PhD Student	100
Raquel Jorge Ferreira Catarino	PhD	Employed HPH	MD	20
Rui Manuel de Medeiros Melo Silva	Agregation	Employed IPO-Porto	TSS	50
Rui Miguel Gil da Costa Oliveira	PhD	Scholarship FCT	Postdoc	40
Ricardo Jorge Correia Pinto	MSc	Scholarship LPCC	PhD Student	100
Daniela Barros Branco	BSc	not employed	MSc Student	100
Diogo Miguel Monteiro Estêvão	BSc	not employed	MSc Student	100
Ines Cristiana Nogueira	BSc	not employed	MSc Student	100

VERTEBRATE DEVELOPMENT AND REGENERATION

GROUP LEADER: **José Bessa**



AIM OF THE GROUP

CREs are essential non-coding sequences required for the proper transcriptional control of genes. The Vertebrate Development and Rregeneration group is dedicated to better understand the mechanisms of cis-transcriptional regulation and how mutations on cis-regulatory regulatory elements (CRE) might impact in the development of some human diseases, in particular pancreatic cancer and diabetes. As a model system we use the zebrafish pancreas. We employ genomic strategies to identify CREs and genetic functional assays to evaluate the function of these sequences.

MAJOR ACHIEVEMENTS IN 2017

Spinocerebellar ataxias (SCAs) are a group of clinically and genetically very heterogeneous diseases, usually characterized by adult onset of progressive gait, limb, and speech ataxia caused by loss of cerebellar neurons. The estimated prevalence of autosomal-dominant SCAs varies considerably in different world regions from 1.6 to 5.6 out of 100,000 inhabitants. Machado-Joseph disease (SCA3) is the most frequent in Portugal and worldwide, but a definite genetic diagnosis is still lacking for more than half of the families affected by these neurodegenerative diseases.

By collaborating with the “Genetics of Cognitive Dysfunction” group, we helped to demonstrate that a mutation in a non-coding transcript induces toxicity in vivo and might be the genetic basis of SCA37. (Seixas et al, Am J Hum Genet. 2017 Jul 6;101(1):87-103. doi: 10.1016/j.ajhg.2017.06.007.)

PUBLICATIONS

Peer-reviewed indexed publications (final publication date in 2017)

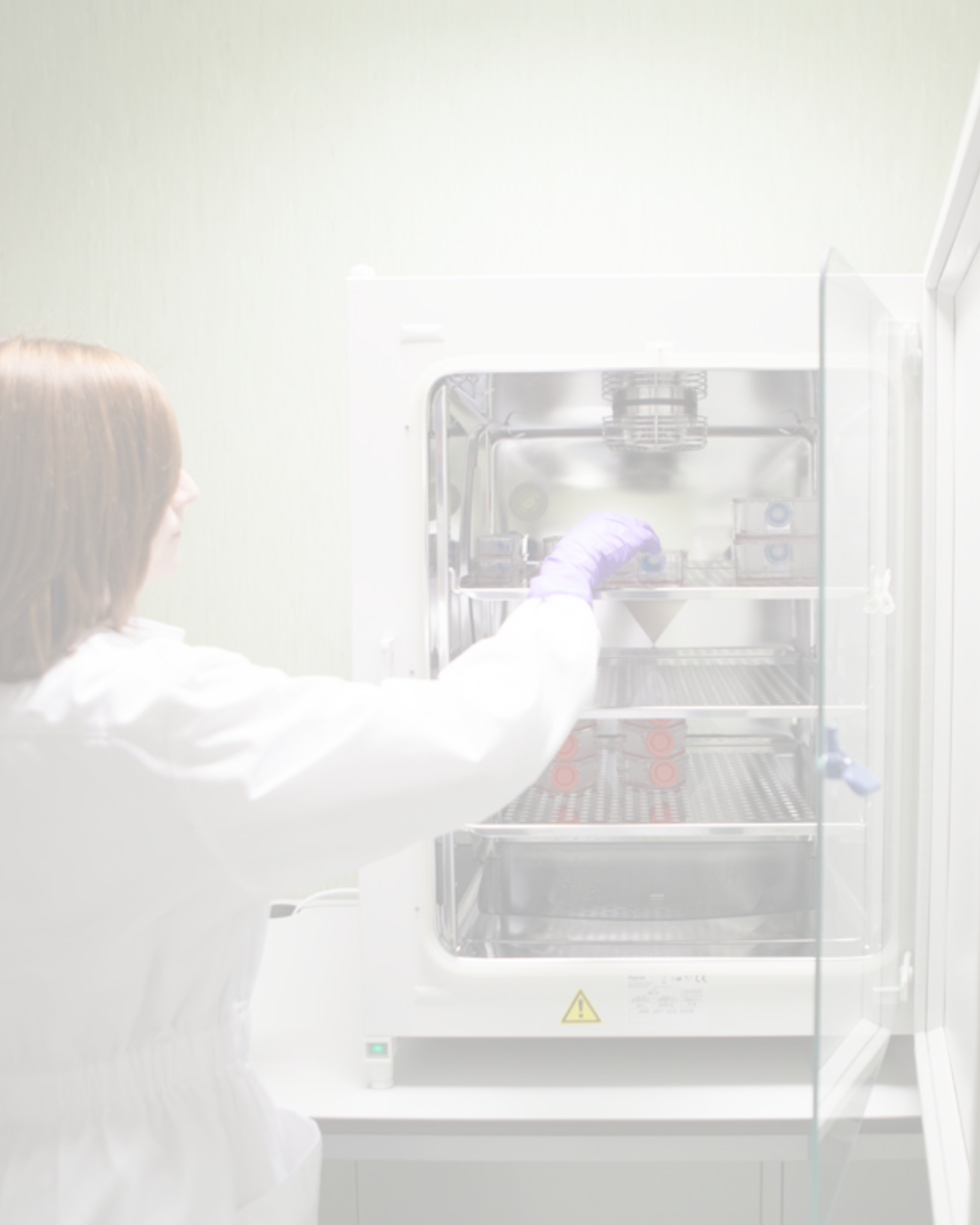
1. Seixas, AI, Loureiro, JR, Costa, C, Ordonez-Ugalde, A, Marcelino, H, Oliveira, CL, Loureiro, JL, Dhingra, A, Brandao, E, Cruz, VT, Timoteo, A, Quintans, B, Rouleau, GA, Rizzu, P, Carracedo, A, Bessa, J, Heutink, P, Sequeiros, J, Sobrido, MJ, Coutinho, P and Silveira, I. A Pentanucleotide ATTTC Repeat Insertion in the Non-coding Region of DAB1, Mapping to SCA37, Causes Spinocerebellar Ataxia. American journal of human genetics. 2017;101(1):87-103 https://www.ncbi.nlm.nih.gov/pubmed/28686858 (Impact Factor: 8.855)

TEAM MEMBERS

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Catarina Macedo Eufrasio	BSc	MSc student	Students	100
Ana Leonor Carvalho	BSc	MSc student	Students	100
Ana Pozo de Dios Gali Macedo	BSc	Research Fellowship (BSc)	Fellows	100
Diogo José Coutinho Ribeiro	BSc	MSc student	Students	100
Joana Filipa Araújo Pinheiro Marques	MSc	Research Fellowship	Fellows	100
Joana Maria Santiago Teixeira	MSc	PhD student	Students	100
João Pedro Curado Agra Amorim	MSc	Research Fellowship	Fellows	100
Marta Duque	MSc	PhD student	Students	100
Marta Ribeiro Jose Cardoso	MSc	PhD student	Students	100
Jose Carlos Ribeiro Bessa	PhD	Principal Researcher	Researchers	100
Renata Cristina Bordeira Costa dos Santos Carriço	PhD	Post-Doc Researcher	Researchers	100
Isabel Maria Lourenço Esteves Moura Guedes	URG	Research Technician	Staff	50
Fabio Júnior Verissimo Ferreira	MSc	PhD student	Students	100

6

CORE FACILITIES SCIENTIFIC PLATFORMS



ADVANCED LIGHT MICROSCOPY UNIT

ANIMAL FACILITY

BIOIMAGING CENTER

BIOCHEMICAL AND BIOPHYSICAL TECHNOLOGIES

BIOSCIENCES SCREENING UNIT

BIOINTERFACES AND NANOTECHNOLOGY

CELL CULTURE AND GENOTYPING SERVICE

GENOMICS CORE FACILITY

HISTOLOGY AND ELECTRON MICROSCOPY SERVICE

IN VIVO CAM ASSAYS UNIT

PROTEOMICS CORE FACILITY

TRANSLATIONAL CYTOMETRY

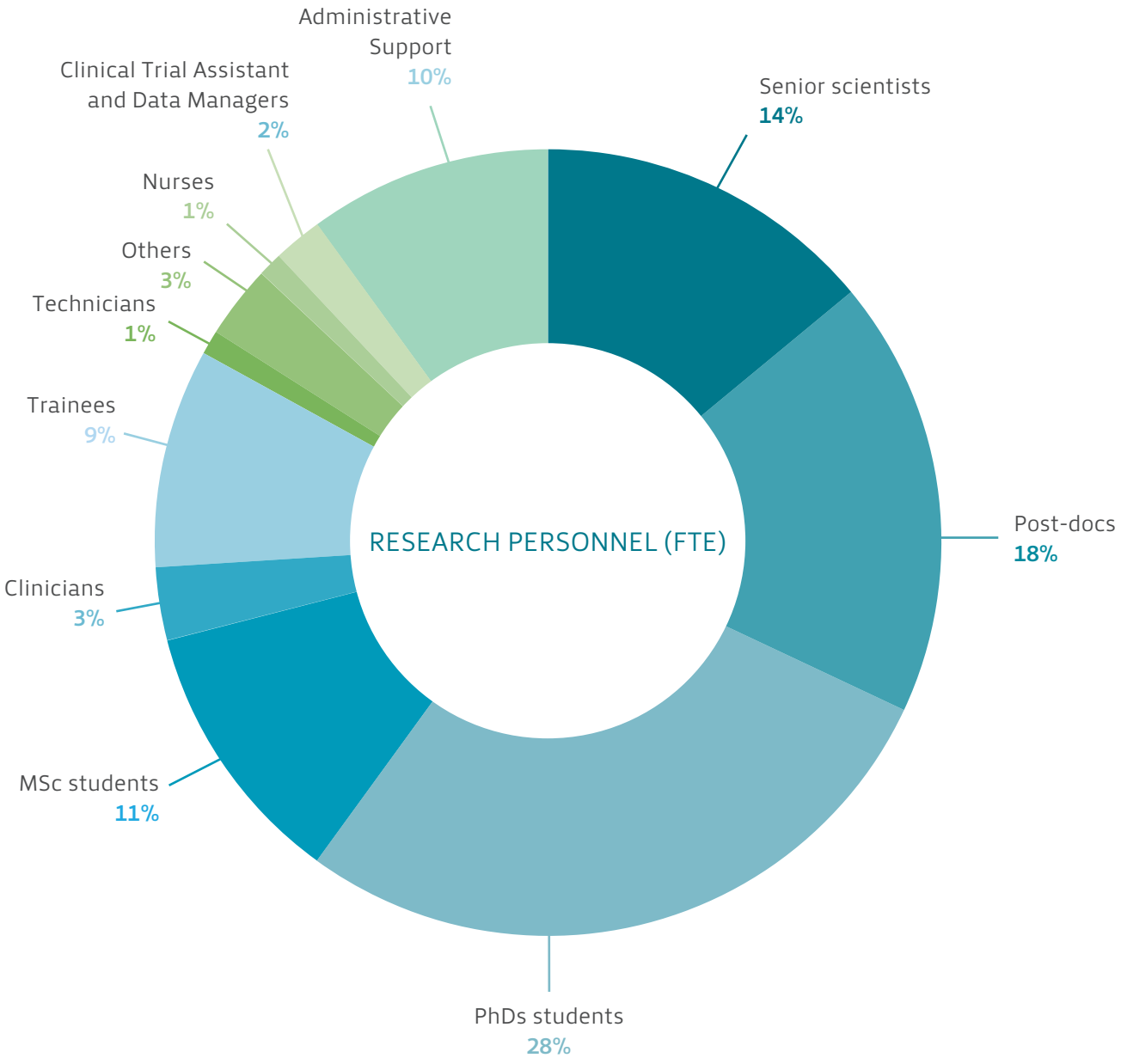
TUMOR BANK

X-RAY CRYSTALLOGRAPHY PLATFORM

7

RESEARCH PERSONNEL (FTE)

Overall, more than 600 persons are directly involved in cancer research at P.CCC.



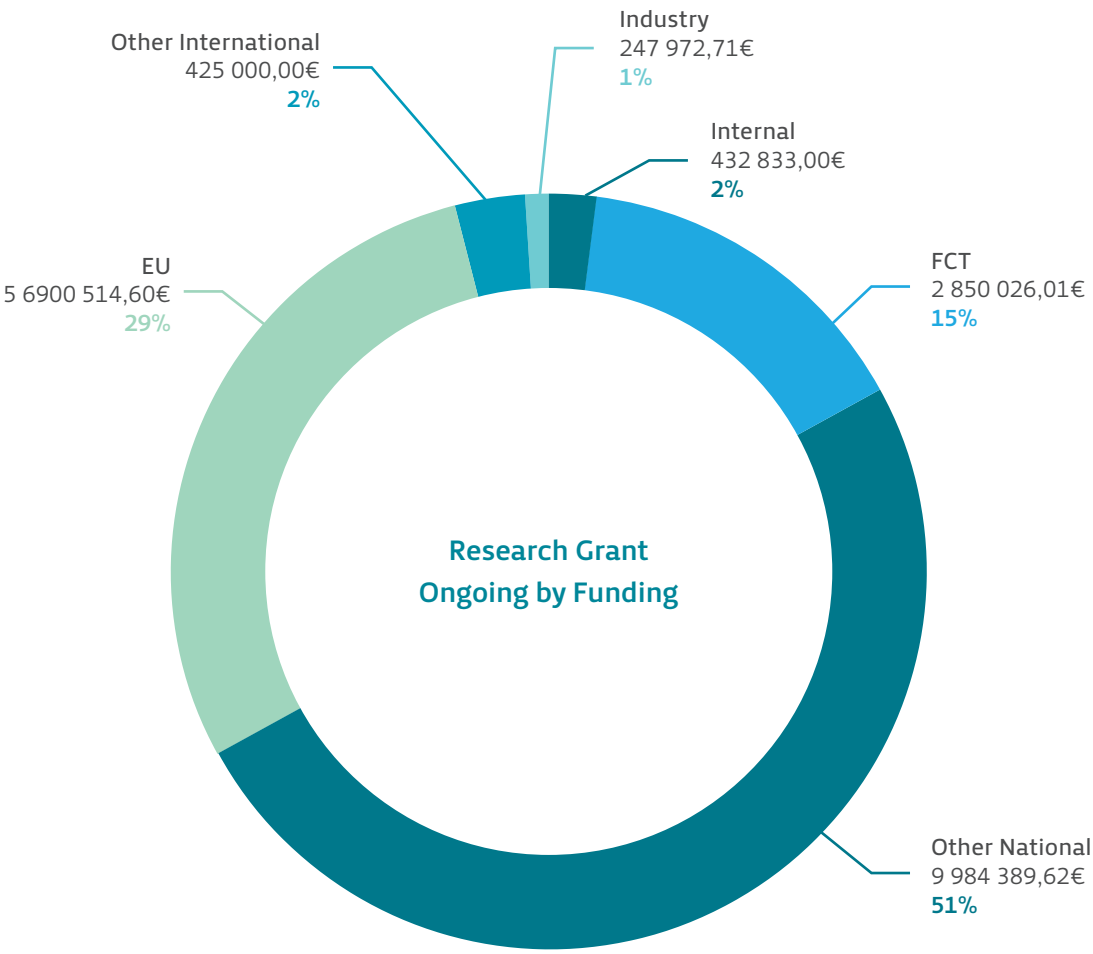
8

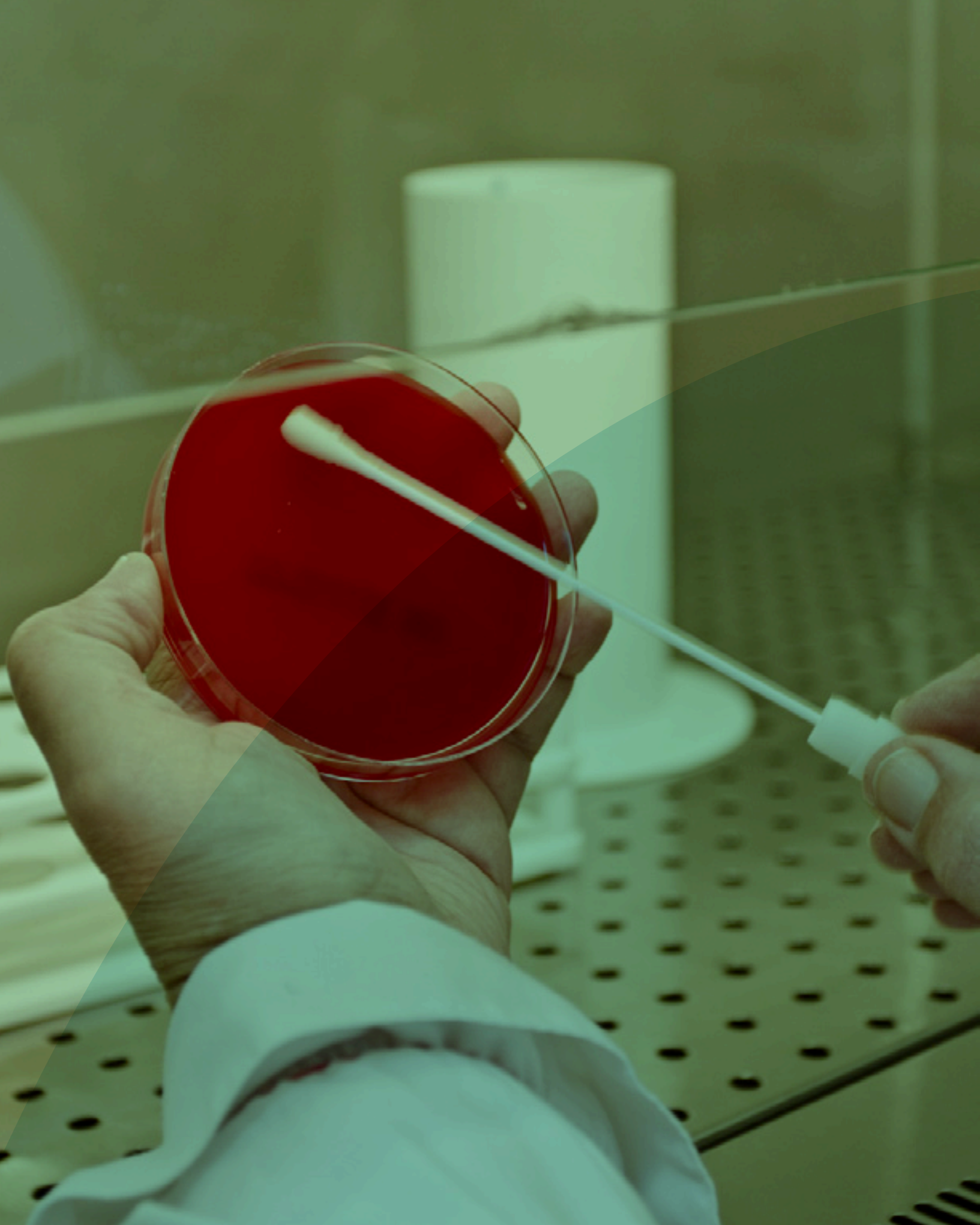
NUMBER FINANCED ONCOLOGY RESEARCH PROJECTS

CANCER RESEARCH GRANTS ONGOING

Funding Agency	Number
Internal	19
FCT	27
Other National	29
EU	6
Other international	4
Industry	5
Total	**90**

The ongoing projects are directly supported by more than 19 Million Euros





9

LIST OF ONGOING PROJECTS

Title	Company Sponsor
3DEMT - A 3D microarray platform for the high-throughput analysis of the role of the extracellular matrix in cancer-associated epithelial-to-mesenchymal transitions	FCT
Advancing cancer research: from basic knowledge to application	NORTE2020
Ageing: cells losing their mitotic fitness and chromosome balance	FCT
An open-label study to investigate the tolerability, pharmacokinetics and anti-tumour effect following photodynamic therapy (PDT) with single-ascending doses of LUZ11 in patients with advanced head and neck cancer" Protocolo LUZ11-CDU-001	Luzitin, SA
Assessment and validation of a panel of methylation-based Biomarkers in cell free DNA for Detection of recurrent first primary cancer (RFPC) and second primary cancers (SPC)	CI-IPOP
Bioengineering of soft tissues through placental extracellular matrices and stem cells of varied origins	CNPq
Biomedical anthropological study in Arabian Peninsula based on high throughput genomics	FCT
Cancel-Stem	Compete2020
Characterisation of the roles of PS3 integrin in Drosophila axonal targeting	NORTE2020
Characterization of Cytomegalovirus Resistant Strains in Hemapoietic Stem Cell Transplanted Patients.	CI-IPOP
Chemical screen for transcriptio nal suppressors of the pancreas oncogene KRAS	NORTE2020
Circulating Viral Genomes in the blood of cervical cancer patients.	CI-IPOP
Clinic, pathologic and molecular study to optimize the treatment of differentiate thyroid carcinoma	SPEDM, IBECATI
CODECHECK	Horizon2020
CyanoPolymerApps- Cyanobacterial extracellular polymeric substances (EPS): From the genes to the industrial toolbox	FCT
Cytoplasmic dynein: mechanisms of regulation and novel interactors	European Research Council
D110204-E-cadherin (Clone 36) Nuclear Staining in Breast Cancer and Comparison with Alternative Clone Staining and P-cadherin staining	ROCHE
Detecção de mutações somáticas no plasma de doentes com cancro do pulmão	INFARMED
Detection of cancer specific genetic alterations in circulating free tumor DNA as a tool for early cancer diagnosis and follow up in Lynch syndrome patients	CI-IPOP
Detection of tumor biomarkers using circulating tumor cell-free nucleid acids/exosomes as a source for biomarkers of intra-tumor heterogenetity	NORTE2020
Development of monoclonal antibodies based in glycobiomarkers as therapeutics for chemoresistent bladder cancer	CI-IPOP
Diabetes & obesity at the crossroads between Oncological and Cardiovascular diseases – a system analysis NETwork towards precision medicine (DOCnet)	NORTE2020

Drosophila screen for modifiers of Myc gain-of-function	NORTE2020
Effects of human ageing and aneuploidy in mitotic fitness and chromosome stability	FCT
Epigenetic signature of prostate cancer stem cells/ Assinatura genética das células estaminais tumorais prostáticas	CI-IPOP
Estaminalidade das células do cancro: um desafio e uma oportunidade para avançar no tratamento em Oncologia	FCT
Estudo Acertive	GEDII
Exome sequencing of families with strong cancer incidence of unknown genetic cause	CI-IPOP
FLAD Grants on Portugal-USA collaborative projects - FLAD Life Science 2020	FLAD Life Science 2020
fMRI na delineação de fOAR em SRS cranial	CI-IPOP
FOLSMART - Folate-Target Nanodevices To Activated Macrophages For Rheumatoid Arthritis	Horizon2020
Gastric microbiota & cancer: more than Helicobacter pylori	Worldwide Cancer Research
Glicoengenharia celular para a avaliação das modificações pós-traducionais dos receptores celulares no cancro	FCT
GlycoCan Marie Curie European Training Network	Horizon2020
GlycoModels: 3D glyco-engineered models to address the role of glycosylation in gastric cancer clinical management	European Union
Glycosylation alterations in cancer cell invasion and metastasis	NORTE2020
Glycosylation of tyrosine kinase receptors as novel biomarkers for targeted therapy	NORTE2020
High-throughput screening to identify novel drugs that override the mitotic checkpoint and induce tumor cell death	NORTE2020
Horizontal transmission of drug resistance: a game changer in the clinical management of cancer patients	FCT
Horizontal transmission of mutation-driven therapy resistance	NORTE2020
HOXB genes function in breast cancer	Compete2020
Human Extracellular Target Validation of HS Members	Pharmaceutical Industry
Identification of biomarkers and molecular targets for multidrug resistant tumors	NORTE2020
Identification of germline mutations by gene-panel next generation sequencing in familial non-medullary thyroid cancer	CI-IPOP
Identification of germline mutations by gene-panel next generation sequencing in familial tubular and mixed tubular-diffuse gastric cancer	CI-IPOP

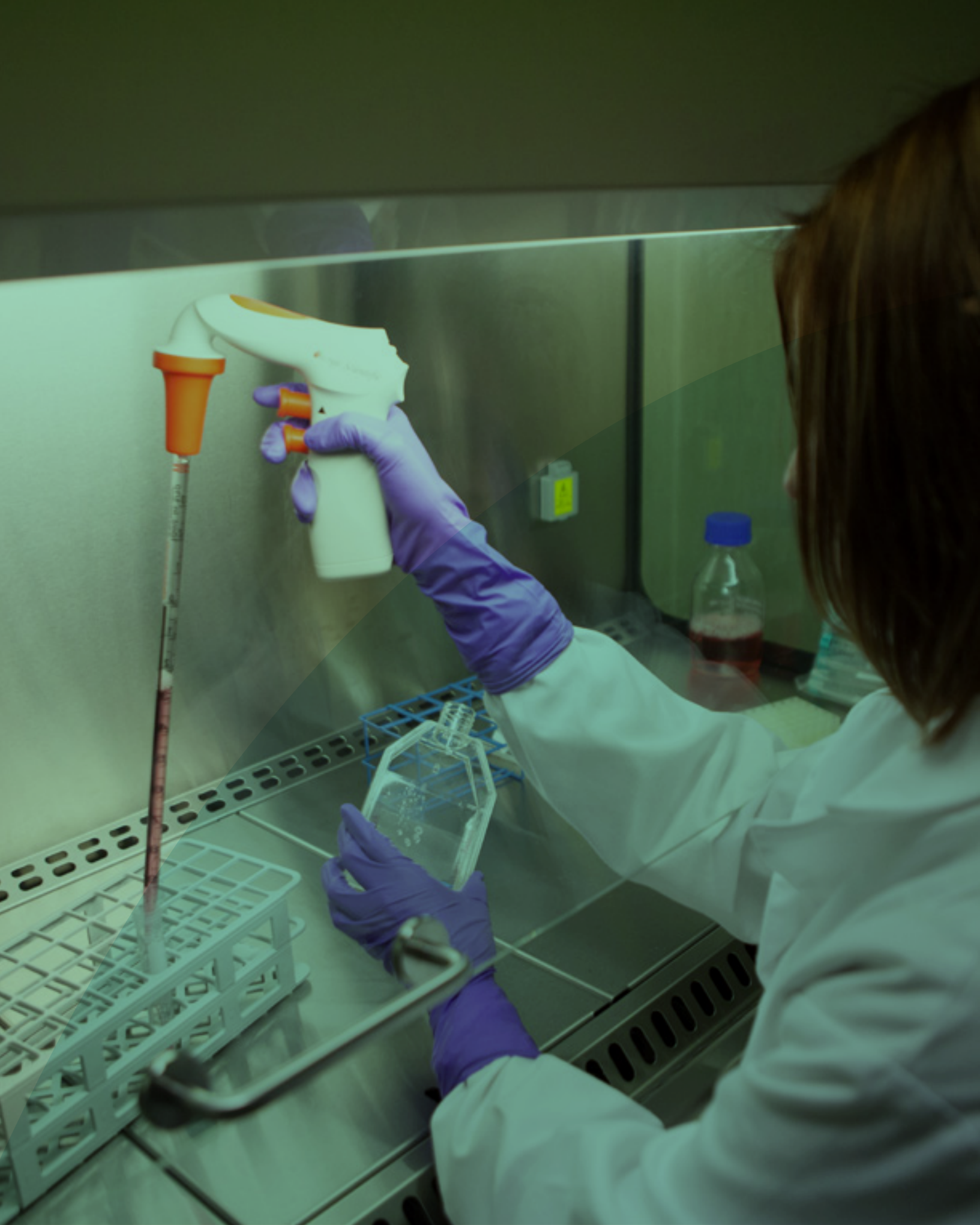
Identification of somatic and germline mutations in circulating tumor DNA in ovarian cancer patients and in germline BRCA1/BRCA2 mutation carriers undergoing cancer screening	CI-IPOP
Identifying microRNAs as biomarkers of drug resistance in Multiple Myeloma patients: a pilot project to contribute to guiding personalized therapeutic decisions	Associação Portuguesa Contra a Leucemia
Identifying susceptibility cancer biomarkers in inflammation prone tumors: stomach and lung models	NORTE2020
Impact of epithelial polarity and adhesion on cell invasion	NORTE2020
Incertezas geométricas em radioterapia externa	CI-IPOP
Inherited predisposition to prostate cancer: finding the missing heritability by combining exome sequencing and haplotype analyses in a population with strong founder effects	FCT
Instituto de Bioengenieria en Red para el Envejecimento Saludable	FEDER
Investigação do papel funcional da osteopontina e de suas variantes de splicing alternativo nos tumores papilares da tireóide	FCT/CAPES
Maratonas da Saúde 2015	Maratonas da Saúde
microRNA-mediated viral regulation of the tumor microenvironment	CI-IPOP
microRNAs as biomarkers of drug response/resistance in multiple myeloma	Sociedade Portuguesa de Hematologia
MK8259-022: An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under golimumab (Evolution)	Merck
Nasythor (Novel natural and synthetic compounds for treating hormone resistant tumors	Norte2020
NEw Targets in DIAstolic heart failure: from coMOrbidities to persoNalizeD medicine	Portugal2020
Novos alvos na insuficiência cardíaca diastólica: das comorbilidades à medicina personalizada	FCT/PAC
P28Nano- Cell penetrating p28 peptide-mediated delivery of nanomedicines for cancer treatment	FCT
Pharmacogenomic Determinants of Therapeutic Response of Urogynecological Cancer: The European Pharmacogenetics Consortium Project (Eu-PIC)	CI-IPOP
Porto Neurosciences and Neurologic Disease Research Initiative at I3S	NORTE2020
PRO-DOSE – Dispositivo para dosimetria in-vivo em braquiterapia	FCT
Proteínas teloméricas dos linfomas de células T cutâneos: potênciais indicadores de tumorigenicidade?	FCT/ Programa Pessoa Porto-Bordeaux
Proteínas teloméricas dos linfomas de células T cutâneos: potênciais indicadores de tumorigenicidade?	CRUP
PYLORIBINDERS-Tratamento/diagnóstico da infecção gástrica utilizando biomaterias específicos para a Helicobacter pylori sem recurso a antibióticos	FCT

Renal cell carcinoma-derived exosome: the microRNA content as a new disease predictive biomarker and an opportunity to invasive/metastatic disease management under the genetic background	CI-IPOP
Resposta Biológica renal em PRRT e dosimetria geral	CI-IPOP
ROle of the MITOchondrial fission protein Drp1 as a prognosis and predictive biomarker in the treatment of differentiated thyroid cancer (ROMITO-DRP1)"	ESAI
Sensing dysfunctional E-cadherin cells in gastric epithelia (SENSE)	FCT
Skinchip - Disruptive cellulose-based microfluidic device for 3D skin modelling	FCT
SkinPrint - In situ skin tissue engineering	FCT
Spatiotemporal control of epithelial architecture during cell division	FCT
Tackling cancer stem cells: a challenge and an opportunity to advance in anti-cancer therapy (CANCER-STEM)	FCT/PAC
Telomerase promoter mutations-consolidation of a multipurpose biomarker	NORTE2020
The functional role of exosomes in tumor hetesogeneity and cancer all plasticity	FCT
The HOXOME of cancer	NORTE2020
The Impact of Aneuploidy on Adult Stem Cell Behavior	FCT
The Pancreas Regulome: From causality to prediction of non-coding mutations in human pancreatic diseases	ERC European Research Council
The role of aneuploidy in the transformation of adult stem cells	NORTE2020
The role of Exosomes in Tumor Heterogeneity: More than Just Bubbling	FCT
The yin and yang of somatic mutations in cancer immunosurveillance	FCT
Today's Present, Tomorrow's Future on the study of germline E-Cadherin Missense Mutations: a step forward on providing informed genetic counseling to everyone	American Association of Patients with Hereditary Gastric Cancer "No Stomach for Cancer"
Towards a single therapy with a synergistic drug combination against triple negative breast cancer and neuroblastoma by nucleoli-mediated multicellular targeting	FCT
Tracing gastric cancer using quantitative bioimaging analysis (TRACE	FCT
Unraveling new regulatory mechanisms of centromere structure, kinetochore-microtubule interaction and spindle assembly checkpoint signaling	FCT
Validation of liquid biopsies for predictive biomarker testing, therapy response monitoring, and resistance mechanism identification in cancer patients	CI-IPOP

10

PROJECTS/ STUDENTS IN COLLABORATION: IPOPORTO & I3S

Title	PI-IPOPorto	PI-IPOPorto PI-I3S	Funding
BRCA-STEM - Exploring stemness in high grade serous carcinoma using hereditary breast-ovarian syndrome as a model system: PhD Student; Rita Canário	Carla Bartosch; (Cancer Biology & Epigenetics) Manuel R. Teixeira (Cancer Genetics)	Joana Paredes (Epithelial interactions in Cancer)	NA
Ethno-oncology initiative: first whole exome sequences from PALOP cancer patients	Lúcio L. Santos (Experimental Pathology and Therapeutics)	Luísa Pereira (GeneticDiversity)	NA
Exploring glycobiomarkers as targets for bladder cancer chemoresistant cells. Pos-doc Project; Luís Lima	Lúcio Lara Santos & Alexandre Ferreira (Experimental Pathology and Therapeutics)	Celso Reis (Glycobiology in Cancer)	SFRH/ BPD/101827/2014
Germline mutations in genes involved in the chromosome segregation machinery associated with inherited prostate cancer predisposition: PhD Student; Maria Pedro	Manuel R. Teixeira (Cancer Genetics)	Hélder Maiato (Chromosomal Instability & Dynamic)	FCT SFRH/ BD/132441/2017
Glycan markers in Gastric Cancer.	Lúcio Lara Santos & Alexandre Ferreira (Experimental Pathology and Therapeutics)	Celso Reis (Glycobiology in Cancer)	NA
Glycobiomarkers in colorectal, lung and ovary cancer.	Rui Henrique & Carmen Jerónimo (Biobank-Department of Patology & Cancer Biology & Epigenetics)	Celso Reis (Glycobiology in Cancer)	NA
HOXB genes function in breast cancer: MSc Student; Mafalda Araújo Pereira	Carmen Jerónimo (Cancer Biology & Epigenetics)	Joana Paredes; (Epithelial interactions in Cancer) Renata Freitas; (Cell Growth and Differentiation)	FCT
Recurrent germline mutations in patients with early-onset and/ or familial prostate cancer, PhD Student; Marta Cardoso	Manuel R. Teixeira (Cancer Genetics)	José Bessa (Vertebrate Development and Regeneration)	SFRH/ BD/116557/2016
TERT mutations in bladder cancer	Lúcio L. Santos (Experimental Pathology and Therapeutics)	Paula Soares (Cancer Signaling and Metabolism)	NA



11

PRIZES, HONOURS AND AWARDS

- ESP Bursary Award for the 29th European Congress of Pathology: Lobo J, Rodrigues A, Antunes L, Graça I, Ramalho-Carvalho J, Quintela-Vieira F, Martins AT, Oliveira J, Jerónimo C, Henrique R. High immunoexpression of EZH2 and SMYD3 in diagnostic prostate biopsies independently predicts outcome in prostate cancer patients.
- "Best Poster Session" in Cytopathology for the 29th European Congress of Pathology: Meireles C, Pires-Luís AS, Lobo J, Carvalho S, Monteiro P, Henrique R, Leça L. Fine needle aspiration cytology of the kidney correlated with histological data: a 17-year retrospective study. 29th European Congress of Pathology, Amsterdam, The Netherlands, 2-6th September.
- João Lobo received the OECI Bursary OECI Bursary Award for the 2nd EACR-OECI Conference "Making it Personal: Cancer Precision Medicine – Amsterdam, Netherlands, March 2017.
- João Lobo received the OECI Bursary Award for the 7th EACR-OECI Joint Training Course "Molecular Pathology Approach to Cancer", Amsterdam, Netherlands, May 2017.
- Teixeira A, Sousa D, Xavier CPR, Vasconcelos MH. Is there horizontal transfer of the oncogene BCR-ABL mediated by extracellular vesicles released by chronic myeloid leukemia cells? 2º Plenary Communication Award in the 12th Young European Scientists (YES) Meeting, Porto, Portugal, 14-17 Setember.
- Castro I, Xavier CPR, Vasconcelos MH. Is P-glycoprotein (P-gp) relevant for the release of microvesicles by tumor cells? Honorable Mention Poster Award in the 12th YES Meeting, Porto, Portugal, September 14-17, 2017.
- Teixeira A, Sousa D, Xavier CPR, Vasconcelos MH. Characterization of Extracellular Vesicles from a pair of drug-sensitive and drug-resistant BCR-ABL positive cell lines.3º Poster Award in the V AEICBAS Biomedical Congress, Porto, Portugal, April 21-23, 2017.
- Castro I, Xavier, Xavier CPR, Vasconcelos MH. Characterization of pairs of drug resistant and drug sensitive cancer cell lines and of their extracellular vesicles.Best Poster Award at the X National Meeting of Biochemistry Students (ENEBIOQ), Universityof Minho, Braga, Portugal, April 7-10, 2017.
- Wilton J, Pereira-Castro I, Freitas J, Costa AM, Castro F, Oliveira MJ, Moreira A. Mechanisms of gene regulation in the crosstalk of the cancer – macrophage microenvironment. SICR2017 – Symposium on Immunomodulation in Cancer & Regeneration, Porto, Portugal, 23 June, 2017.
- Inês Almeida received the Medal of Honor for Women in Science (FCT/UNESCO/L´OREAL)
- 1st prize of "BfK IDEAS 2017" - Born from Knowledge, Agência Nacional de Inovação, Project MyRNA (Diagnosis of depression); Inês Almeida, Susana Santos, Inês Alentaste, Sofia Esteves and Barbara Macedo, Portugal.
- Raquel M. Gonçalves received an "Humboldt Fellowship for Experienced Researchers", Alexander Humboldt Foundation, 2017
- Luzia Garrido to first author; Carla Oliveira Senior author received the SPGH Meeting "Prof. Doutor Amândio Tavares, FWA Award" for the best basic research work in Oncogenetics and Public Services in, Porto, Portugal, 2017.
- Celina São José (Master student in Oncology) received "Best Poster Award" from V Aeicbas Biomedical Congress/ICBAS, Porto, Portugal, 2017.
- Joana Carvalho received"Travel Grant Award" United European Gastroenterology week, Barcelona, Spain, 2017.

- **External consultant for the Ministry of Health, Portugal (Luís Pedro Resende)**

- **Secretary General of the international Glycoconjugate Organization (IGO) from 2017 to 2019 (**http://www.intl-glyco.org/officers.html**) (Celso Reis)**


IPOPORTO
Para cuidar de si!
INSTITUTO PORTUGUÊS DE ONCOLOGIA-PORTO

12

INTERNATIONAL COLLABORATION

RESEARCH CONSORTIA

CIMBA: The Consortium of Investigators of Modifiers of BRCA1/2 - a collaborative group of researchers working on genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers (coordinated by Georgia Chenevix-Trench, PhD, Queensland, Australia).

IMPACT: Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls (coordinated by Ros Eeles, MD, PhD, London, UK).

PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome - a collaborative group of researchers interested in inherited risk of prostate cancer (coordinated by Ros Eeles, MD, PhD, London, UK).

BCAC: The Breast Cancer Association Consortium – a forum of investigators interested in the inherited risk of breast cancer (coordinated by Doug Easton, PhD, Cambridge, UK).

COGENT: COlorectal cancer GENeTics – a collaborative group of researchers working on inherited predisposition of colorectal cancer. EU funding by COST Action BM1206: Cooperation Studies on Inherited Susceptibility to Colorectal Cancer (coordinated by Sergi Castellví-Bel, PhD, Barcelona, Spain).

EPICHEM: Epigenetic Chemical Biology – a collaborative group of researchers working on epigenetic drugs. EU funding by COST Action CM1406 (coordinated by A Ganesan, PharmD, PhD, Norwich, UK).

EPITRAN: Epitranscriptomics Network- a collaborative group of researchers working on epitranscriptomics. EU funding by COST Action CA16120 (coordinated by Alessandro Quattrone, PhD, University of Trento, Italy).

IGO: International Glycoconjugate Organization (President, Prof. Jianxin Gu, China). The aims of the International Glycoconjugate Organization (IGO) are: 1. to further international collaboration for the study of glycoconjugates; 2. to ensure the proper arrangement of the biennial International Glycoconjugate Symposia; 3. to select recipients of the IGO Award and the IGO Young Glycoscientist Award as well as administer the Award Fund.

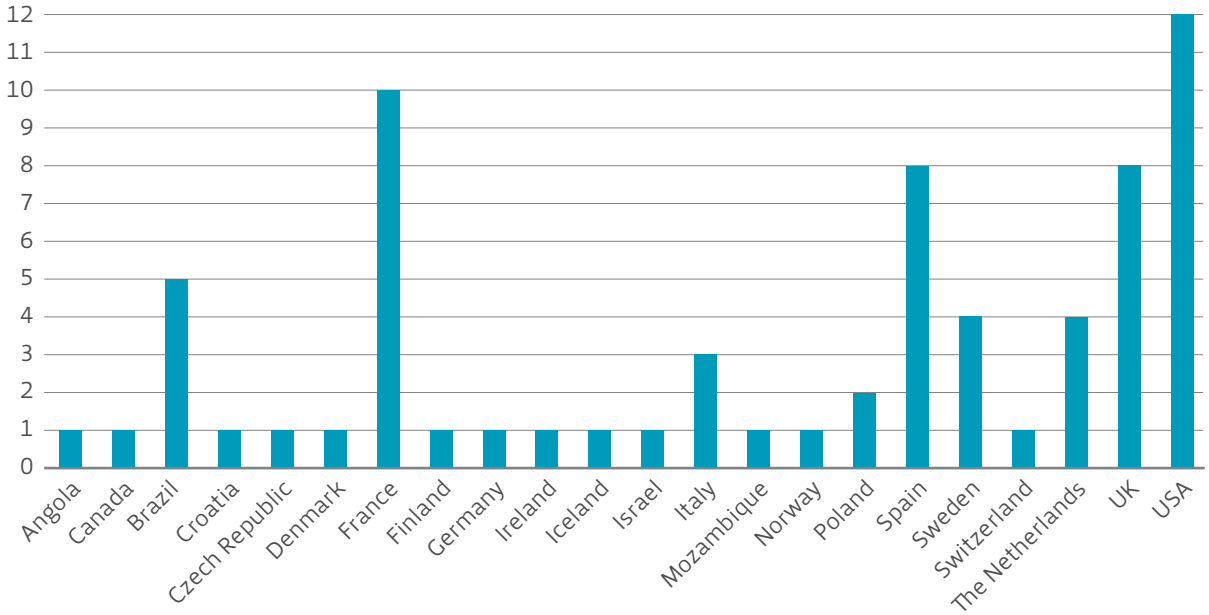
ME-HAD: European Network on Microvesicles and Exosomes in Health and Disease. A collaborative group of researchers fostering a multidisciplinary approach to enhance basic understanding and translational potential of Microvesicles and exossomes. EU funding by COST Action BM1202 (coordinated by Lorraine O'Driscoll, PhD, Dublin, Ireland).

StemChem: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells. a collaborative group of researchers working on drug design and the medicinal chemistry of synthetic and natural compounds and investigators dedicated to the understanding the mechanisms governing drug resistance in cancer stem cells. EU funding by COST Action CM1106 (coordinated by Daniele Passarella, PhD, Milano, Italy).

Genturis ERN: European Reference Network (ERN) for GENetic TUmour RIsk Syndromes (GENTURIS) on CDH1-related Hereditary Diffuse Gastric Cancer. This consortium aims to improve the identification, diagnosis and surveillance of a wide range of rare inherited syndromes, predisposing to tumour development at any stage during life.

Individual groups have collaborative networks that are reflected in the intense co-authorship in publications. Some collaboration has been intense and stable, and those are the ones listed below:

International Collaborations Ongoing



ANGOLA
Clinica Sagrada Esperança, Luanda

CANADA
British Columbia Cancer Agency, Vancouver, Canada

BRAZIL
Barretos Cancer Hospital, S. Paulo, Brazil
Experimental Research Center, Clinical Hospital of Porto Alegre, Porto Alegre, Brazil
National Cancer Institute Instituto Nacional do Cancer (INCA), Rio de Janeiro, Brasil
Universidade Federal de Minas Gerais, Belo Horizonte, Brasil
Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

CROATIA
Bošković Institute, Zagreb

CZECH REPUBLIC
Nuclear Physics Insitute Prague,

DENMARK
Faculty of Health Sciences of the University of Copenhagen

FRANCE
Centre National de la Recherche Scientifique (CNRS); Laboratory Epigenetic Targeting of Cancer (ETaC), Toulose
IARC, Lyon
INSERM, Grenoble
INSERM, Hôpital Saint-Antoine, Paris, France
INSERM, Nantes, France
INSERM, Strasbourg, France
Institut Pasteur, France
Institut de Radioprotection et de Surete Nucleaire (IRSN), Paris
University of Lille
Université Toulouse III, Université de Toulouse
Sorbonne Universités, UPMC Université.

FINLAND
University of Helsinki, Helsinki

GERMANY
University Hospital, Heidelberg

ICELAND
deCODE Genetics/Amgen, Reykjavik

IRELAND
Dublin City University & National Institute for Cellular Biotechnology, Dublin

ISRAEL
Weismann Institute, Rehovot, Israel

ITALY
Cluster in Biomedicine, Trieste
University of Bologne
University of Siena

MOZAMBIQUE
Hospital Central Maputo

NORWAY
Institute for Cancer Research of the Norwegian Radium Hospital of Oslo University Hospital

POLAND
Instytut Fizyki Jadrowej, Krakow
National Centre for Nuclear Research, Swierk

SPAIN
Catalan Institute of Oncology, Barcelona
Complexo Hospitalar Universitario, Vigo
Universitat de Lleida, IRBLleida, Lleida
Universitat Autònoma de Barcelona, Spain
University of Navarra
University of Santiago de Compostela, Santiago de Compostela
Universitat Politecnica de Catalunya, Barcelona
Murcia BioHealth Research Institute-Hospital “Virgen de la Arrixaca” (IMIB-Arrixaca)
University of Cordoba

SWEDEN
Karolinska Institute, Stockholm, Sweden
Umea University
University of Gothemburg
University of Uppsala, Uppsala

SWITZERLAND
University of Lausanne

THE NETHERLANDS
Erasmus University, Medical Center Rotterdam
The Netherlands Cancer Institute, Amsterdam
University Nijmegen Medical Centre
University of Groningen

UK
Cancer Research UK Beatson Institute, Glasgow, Scotland
Imperial College Faculty of Medicine, London
King's College London
Paterson University of Manchester, Manchester
University College London, London
University of Cambridge
University of Leicester & Leicester University Hospitals
University of Newcastle upon Tyne & formerly Newcastle Freeman Hospital

USA
Cancer Center & Louisiana State University
Center for Cancer Research, National Cancer Institute, Bethesda
Cincinnati Children’s Hospital
Department of Cell Biology, Harvard Medical School, Boston
Geisel School of Medicine, Dartmouth College, Hanover
Massachusetts General Hospital, Boston
Massachusetts Institute of Technology (MIT), Cambridge
Memorial Sloan-Kettering Cancer Center, New York
University of Miami
University of Michigan
University of Nebraska Medical Center
University of Texas

13

INNOVATION

START-UP/TRANSFER OF KNOWLEDGE

I3S has a dedicated technology transfer Unit with the mission to create value from the commercial exploitation of intellectual property (I.P.) and to stimulate the creation and growth of spin-off companies based at IPATIMUP/I3S. Through consulting and coaching, the Innovation Unit helped researchers achieve the different steps in the innovation cycle of services and products derived from their core research activities. The Innovation Unit undertakes four main lines of action: 1) Registration of I.P. and Licensing to established companies; 2) Application to Innovation funding programs/awards; 3) Launching of new spin-off companies; 4) Direct presentation of projects to Venture Capitals and investors.

The Unit provides support to all steps of registration and exploitation of IP, through experts in IP with strong scientific background and previous experience in licencing IP to established companies. In the cancer research field we have licensed 3 proprietary products/methods/technologies.

We have partnerships with companies in the framework of innovation-oriented research:

- Targetalent, co-promotion project to develop Digital cytology-based diagnostic platform for oral cancer;
- U-monitor, research for development and clinical validation of urine-based method for bladder cancer surveillance.
- The technology transfer unit supports all steps of business development, from idea to market.

PATENTS

Description	File number
Ferreira JA, Dieguez L, Oliveira M, Neves M, Ribeiro R, Reis CA, Santos LL. Strategy and microfluidics device for detection and isolation of cancer cells from body fluids based on a glycosylation pattern and methods of use thereof. . 2017, May 25	File number PAT 110101

14

EDUCATION AND ADVANCED TRAINING

PHD PROGRAMMES

- Biomedicine (FMUP)
- Biotech Health (ICBAS, FFUP, INEB, IBMC, IPATIMUP, Requimte, CHP)
- GABBA (ICBAS, FMUP, FCUP, IBMC, INEB, IPATIMUP)
- Molecular and Cellular Biology (ICBAS, IBMC)
- Molecular Oncology and Medicine (FMUP/ICBAS)
- Pathology and Molecular Genetics (ICBAS, FMUP)

MSC PROGRAMMES

- Biochemistry (ICBAS/FCUP)
- Integrated M.Sc. course in Bioengineering (ICBAS/FEUP)
- Integrated M.Sc. course in Medicine (ICBAS)
- Integrated M.Sc. course in Medicine (FMUP)
- Integrated M.Sc. course in Veterinay Medicine (ICBAS)
- Medical Physics (FCUP)
- Molecular and Cellular Biology (ICBAS, IBMC)
- Molecular Oncology and Medicine (FMUP)
- Oncology (ICBAS/IPO Porto)

ADVANCED COURSES

- Workshop on Cancer Research (IPATIMUP-I3S/ICBAS)
- Institut Curie/Institut Pasteur, Molecular Biology of the Cell Course, 2017, Paris, France (I3S).
- Course on Cell Culturing; 2 editions: May and September(IPO Porto)
- Hands-on Course | Introduction to Biological Data Analysis with R (IPATIMUP-I3S)

MSC DISSERTATIONS

Overall, 43 MSc dissertations in cancer research were completed at Porto.CCC.

Name	Fellowship	Title	Program	Faculty/University	Supervisor team	Public defense
Adriana Costa	NA	Acquisition and Optimization of LU-177 DOTATE planar image with SIMIND Monte Carlo simulations	Master in Medical Physics	Faculty of Sciences of the University of Porto	João Santos	30/11/2017
Alexandra Teixeira	NA	Evidence for BCR-ABL oncoprotein packaging into extracellular vesicles released by BCR-ABL+ leukemia cells: possible implications on cellular response to STI571	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	M. Helena Vasconcelos; Cristina Xavier	24/11/2017
Alexandre Dias	Fellowship	Characterization of The Rna-Binding Protein MEX3A In Mouse Stomach	Genetics and Molecular Medicine	Nova Lisboa University	Raquel Almeida; Bruno Pereira	-/11/2017
Ana Catarina Rocha	NA	Germline and somatic ALK alterations in neuroblastoma patients	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Manuel Teixeira; Ana Peixoto; Joana Vieira	12/12/2017
Ana Isabel da Rocha Sá	NA	Evaluation of a novel mouse model of pancreatic neuroendocrine tumors	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	João Vinagre; Paula Soares	12/12/2017
Ana Laura Costa	NA	DNA Methylation Profiling as a tool for Testicular Germ Cells Tumors Subtyping	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Henrique; Carmen Jerónimo	13/12/2017
Ana Rita Ribeiro Pinho	IPO employee	Dosimetric predictors of acute hematologic toxicity during concurrent chemoradiation for anal cancer	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Isabel Bravo	29/11/2017
André Pina	NA	Evidence for a role of autophagy in the release of extracellular vesicles by tumour cells: possible implications for drug resistant cells with impaired autophagy	Master in Biochemistry	Institute of Biomedical Sciences Abel Salazar of the University of Porto	M. Helena Vasconcelos, Cristina Xavier	16/11/2017
Andreia Oliveira	NA	Optimization of an in-vivo verification system using TLD dosimetry –metrological validation using the ISO 28057:2014 standard	Master in Medical Physics	Faculty of Sciences of the University of Porto	João Santos; Anabela Dias	28/11/2017
Ângela Marques-Magalhães	NA	Anti-neoplastic activity of newly synthetized DNMTi in urological tumors	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Inês Graça	03/11/2017
Carlos Guimarães	NA	Cancer-associated fibroblasts and tumor-associated macrophages: exploring their mutual regulation	Master on Bioengineering – Molecular Biotechnology branch	Faculty of Engineer/ Institute of Biomedical Sciences Abel Salazar University of Porto	Sérgia Velho	30/02/2017
Carolina Paredes	NA	Silk Fibroin based scaffolds produced via 3D bioprinting and electrospinning		University of Trás-os-Montes and Alto Douro	Aureliana Sousa; Marco Araújo; Victoria Zea Bérmudez	-/09/2017
Catarina Moreira-Barbosa	NA	A DNA-methylation signature by MULTIPLEX METHYLIGHT for Prostate Cancer Diagnosis and Prognostication	Molecular Medicine and Oncology	Faculty of Medicine of the University of Porto	Carmen Jerónimo; Rui Henrique	13/01/2017
Celina São José	NA	The Germline and Somatic Landscape of Familial Intestinal Gastric Cancer: Search for a Cause	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carla Oliveira; Joana Carvalho	21/11/2017
Dalila Augusta Lopes	NA	Molecular Imprinting as a tool for producing molecularly intelligent scaffolds for Tissue Engineering	Integrated Master in Biomedical Engineering	Tecnology Sciences Faculty Nova Lisboa University	Goretti Sales; Aureliana Sousa	15/11/2017

Name	Fellowship	Title	Program	Faculty/University	Supervisor team	Public defense
Daniela Barros-Silva	NA	MicroRNA-27a-5p Regulation by Promoter Methylation and MYC Signalling in Prostate Carcinogenesis	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Rui Henrique	04/10/ 2017
David Bidarra	NA	Circulating microRNAs as Markers of Prostate Cancer Progression: a time-based approach	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Rui Henrique	02/12/2017
Diana Pádua	NA	Isolation and characterization of gastric cancer stem cells based on SOX2/OCT4 activity	Master in Biochemistry	Faculty of Sciences & Institute of Biomedical Sciences Abel Salazar of the University of Porto	Raquel Almeida; Rita Barros	16/11/2017
Eliana Janine Paiva Soares	NA	CD-44-glycoprofilling: Establishing the molecular basis for targeted therapeutics in bladder cancer	Master in Clinical Biochemistry	University of Aveiro	Alexandre Ferreira; Luís Lima	22/11/2017
Hugo Girão	FLAD Life Science 2020	CLASP2 functional domains - role in kinetochore microtubule dynamics and mitotic fidelity	Master in Cellular and Molecular Biology	Faculty of Sciences of the University of Porto	Helder Maiato	12/16/2017
Inês Sarmento Ruivo Pinheiro Monteiro	NA	Association between nutritional status and post-surgical complications in patients of Digestive and Head and Neck referred for intermediate and intensive care of the Pathology Units	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Lúcio Santos	04/12/2017
Joana Catarina Pereira Meireles Gonçalves	NA	A genetic study of male infertility centered in semen hyperviscosity and asthenozoospermia phenotypes	Master in Biochemistry	Faculty of Sciences of the University and Institute of Biomedical Sciences Abel Salazar of the University of Porto	Susana Seixas	07/12/2017
Joana Pereira	NA	Targeting anoikis resistant P-cadherin enriched breast cancer cells by in vitro metabolic reprograming	Master in Molecular Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Joana Paredes	31/10/2017
Joana Safira Santos	NA	Uncertainties quantification and methodology comparison for in vivo measures intraoperative radiation therapy	Master in Medical Physics	Faculty of Sciences of the University of Porto	Sandra Sarmento Sofia Silva	12/12/2017
João Abel Rainho Fonseca	NA	Exploring the role of proteolysis in Extracellular Matrix remodeling: Links to Chronic Obstructive Pulmonary Disease and Lung Cancer	Master in Molecular Genetics and Biomedicine	Tecnology Sciences Faculty Nova Lisboa University	Susana Seixas	16/11/2017
João Alexandre Ribeiro de Almeida	NA	Co-expression networks between protein encoding mitochondrial genes and all the remaining genes in human tissues	Informatics and Computational Engineering	Faculty of Enginnering of the University of Porto	Luísa Pereira; Rui Camacho	14/07/2017
João Luís Martins da Gama	NA	Expression of histone modifying enzymes as prognostic biomarkers in follicular lymphoma	Integrated MSc in Medicine	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Henrique	-/07/2017
Jorge Oliveira	NA	Clinical implementation of Monte Carlo Simulations of a True Beam Unit	Master in Medical Physics	Faculty of Sciences of the University of Porto	Alessandro Esposito; João Santos	16/11/2017
Jose Manuel Ferrer Martinez	NA	Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia patients: retrospective cohort study	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros; Ana Espírito Santo	11/11/2017
Liliana Pereira Santos	NA	Role of mitochondrial dynamics in Hürthle cell tumours: Coupling, uncoupling and fission	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Valdemar de Jesus Conde Máximo	05/12/2017

Name	Fellowship	Title	Program	Faculty/University	Supervisor team	Public defense
Luísa Maria Russo Prada	NA	Immunohistochemical characterization of basal cell carcinomas in irradiated and non-irradiated individuals	Integrated Master in Medicine	Medicine School; University of Braga	Paula Boaventura; Paula Soares	
Maria Amorim	NA	Decoding the usefulness of miRNAs as predictive biomarkers in breast cancer patients treated with endocrine therapy	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Rui Henrique	04/10/2017
Maria Margarida Feliciano Silvestre Ferreira	NA	Analysis of a polymorphism in the serotonin transporter gene (5-HTTLPR) in individuals from the Alentejo zone and its relation to suicidal behavior	Master in Legal Medicine	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros	24/11/2017
Mariana Gomes Morais	NA	GLUT-1 related microRNAs and glycolysis in clear cell renal cell carcinoma	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros	07/12/2017
Pedro Nunes	NA	Establishing a protocol for detection of Acute Myeloid Leukaemia Markers in Liquid Biopsies Based on Extracellular Vesicles	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	M. Helena Vasconcelos; Hugo Caires; Manuel Areias Sobrinho Simões	24/11/2017
Rafael Amorim	NA	Histone post-translational modifications and chromatin remodelers in colorectal cancer	Integrated Master in Medicine	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Rui Henrique	18/05/2017
Ricardo Jorge Correia Pinto	NA	Genome-wide association studies and clinical outcome in ovarian cancer patients: validation in an independent cohort	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros	27/11/2017
Silvana Ferreira da Silva Miranda	IPO employee	The role of mitochondria in the non-target effect of ionizing radiation	Master in Medicine and Molecular Oncology	Faculty of Medicine of the University of Porto	Paula Boaventura; Valdemar de Jesus Conde Máximo; Anabela Dias	14/11/2017
Sofia Paupério Paulino	NA	Epigenetic biomarkers in diffuse large B-cell lymphoma	Master in Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Henrique; Carmen Jerónimo	12/12/2017
Susana Margarida Oliveira Gonçalves	IPO employee	Design and production of individualized boluses for external radiotherapy via three-dimensional printing	Master in Biomedical Engineering	Faculty of Engineering of the University of Porto	Anabela Dias	20/10/2017
Vera Antunes	IPO employee	Development of an advanced partition model dosimetry system for hepatic radioembolization using Y-90 microspheres	Master in Medical Physics	Faculty of Sciences of the University of Porto	João Santos	28/11/2017
Vítor Filipe Oliveira Teixeira	NA	Deep Learning for genomic data analysis	Master in Informatics	Faculty of Engineering of the University of Porto	Rui Camacho; Pedro Ferreira	-/09/2017
Yara Priscilla Pedro Bule	NA	Human Papilloma Virus in University Students in Maputo. Mozambique: Using an Auto-Harvest Method	Master in Medicine and Molecular Oncology	Faculty of Medicine of the University of Porto	Rui Medeiros	11/12/2017

PHD THESES

Overall, 23 PhD theses in cancer research were completed at Porto.CCC.

Name	Fellowship	Title	Program	Faculty/University	Supervisor team	Public defense
Alexandre Pedro Tavares da Fonseca Magalhães	NA	Association between Urban Environment, physical and sport activity in teenagers in Porto Municipality	Public Health	Faculty Of medicine of the University of Porto	Fátima Pina	01/02/2017
Ana Catarina Gomes Tavares	NA	The pathogenic role of mTOR pathway in papillary thyroid carcinoma and its impact on sodium iodide symporter (NIS) expression	Molecular Medicine and Oncology	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Paula Soares	18/09/2017
Ana Catarina Leite Pereira	SFRH/ BD/ 85779/ 2012	Mesenchymal stem/stromal cells recruitment for invertebral disc regeneration	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Mário Barbosa; Raquel Gonçalves	19/07/2017
Ana Sadio	Fellowship Gulbenkian/ Champalimaud	Delivery of siRNAs directed to CDX2: a strategy to revert gastric intestinal metaplasia	Medicine and Molecular Oncology	Faculty of Medicine of the University of Porto	Raquel Almeida; Ana Paula Pêgo	21/12/2017
Ana Sílvia Luís	FCT: SFRH / SINTD/ 94217/ 2013	Definition of new biomarkers with potential clinical application based on the epigenetic profile of renal tumors	Molecular Medicine and Oncology	Faculty of Medicine of the University of Porto	Rui Henrique; Carmen Jerónimo	07/11/2017
Ana Sofia Varanda	FCT	Unravelling The Cellular Networks That Regulate Proteotoxic Stress	Biomedicine	University of Aveiro	Carla Oliveira; Manuel Santos	-/03/2017
Arantxa Blázquez Prunera	IB2 - Marie Curie: FP7-PEOPLE-2012-ITN (317052)	Effect of a good-manufacturing-practice xeno-free medium on mesenchymal stromal cell properties: Multipotentiality, Immunomodulation and Recruitment	Biomedical Engineering	Faculty of Engineering of the University of Porto	Catarina Almeida; Susana Santos; Mário Barbosa	06/12/2017
Carla M. Magno Bartosch	NA	Genetic-environmental interaction in the pathogenesis of endometrial epithelial tumors: the importance of epigenetic changes	Molecular Medicine and Oncology	Faculty of Medicine of the University of Porto	Jose M. Lopes; Carmen Jerónimo	03/10/2017
Catarina Marques	NA	Design and processing of porous scaffolds based on calcium phosphates by robocasting for bone tissue engineering		University of Porto	Aureliana Sousa; José Maria Ferreira	19/12/2017
Danica Drpic	FCT	The role of chromosome arms and kinetochore architecture in the formation of amphitelic attachments - Implications for mitotic fidelity	GABBA	University of Porto	Helder Maiato	29/05/2017
Daniel Fernando Marques de Vasconcelos	SFRH/ BD/ 87516/ 2012	Immune response to biomaterials: modulating inflammation towards improved performance of medical devices	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Mário Barbosa; Susana Santos; Meriem Lamghari	24-07-2017
Graciosa Patrícia Quelhas Teixeira	SFRH/ BD/ 88429/ 2012	Modulation of inflammatory response associated with intervertebral disc degeneration	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Raquel Gonçalves; Mário Barbosa	19/07/2017
Jani Viviana Alves Vital da Silva	NA	Sexually transmited infections in women of reproductive age: epidemiology, risk factors and genetic susceptibility profile	Biomedicine	Faculty of Medicine, University of Porto	Rui Medeiros	11/12/2017
João A. Ramalho-Carvalho	FCT: SFRH/ BD/ 71293/2010	MicroRNAs regulation of Chromatin Structure in Prostate cancer	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carmen Jerónimo; Rui Henrique; Manel Esteller	09/06/2017

Name	Fellowship	Title	Program	Faculty/University	Supervisor team	Public defense
Juliana Rosa Dias	NA	Hierarchical electrospun nanostructures for skin regeneration	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Pedro L. Granja; Paulo Bártolo	27/11/2017
Lígia Maria Correia de Araújo Almeida	FCT	"Clinical, histological, and genetic characterization of papillary renal carcinoma (PRCC): diagnostic and therapeutic implications"	Pathology & Molecular Genetics	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Valdemar de Jesus Conde Máximo; José Manuel Lopes; Paula Soares	20/03/2017
Maria Deolinda Paulino Pereira de Sousa Pereira	NA	Ovarian carcinoma: polymorphisms of glutathione S-transferase and implications in therapeutic options - from clinical to molecular biology	Medical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros	10/07/2017
Marisa Gomes Domingues dos Santos Saraiva	NA	Locally advanced rectal cancer: prognostic factors and their implications for therapy and outcomes	Medical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Carlos Lopes; Lúcio Lara Santos	17/11/2017
Marta Neto	PPCDT/ BIA-BCM/ 56043/2004	Regulation of quasi-stable cell states by the Brahma complex subunit Bap60 during eye development	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Fernando Casares; Paulo Pereira	16/06/2017
Mónica Patrícia Silva Gomes	NA	Molecular study of a profile of inflammatory mediators associated with the development and behavior of lung cancer: molecular epidemiology and pharmacogenomics	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Rui Medeiros	18/12/2017
Nádia Eusébio	SFRH/BD /95087/2013	Developmental regulation and functions of the TGFβ signaling pathway in Drosophila melanogaster	Biology	Faculty of Sciences of the University of Porto	Paulo Pereira; Fernando Tavares	06/07/2017
Nuno Silva de Morais Neves	NA	Strontium rich hybrid injectable system for bone regeneration	Medicine	Faculty of Medicine, University of Porto	Mário Barbosa; Cristina Ribeiro	20/12/2017
Pedro Miguel Teixeira Pinto	SFRH/BD /73719/2010	Phenotypic and genotypic heterogeneity of hereditary breast and ovarian cancer	Biomedical Sciences	Institute of Biomedical Sciences Abel Salazar of the University of Porto	Manuel Teixeira; Ana Peixoto	05/05/2017


40x
50x
100x

15

SCIENTIFIC DIFFUSION

ORGANIZATION OF INTERNATIONAL CONFERENCES

- 6th China-Europe Symposium on Biomaterials in Regenerative Medicine, April, 21-24, 2017, Porto (Local Organizing Committee)
- 12th Jenner Glycobiology and Medicine Symposium "Translational Glycobiology – From Bench to Bedside" May 6-9, 2017; Dubrovnik, Croatia (Member of the Scientific Advisory Board)
- 2nd Symposium on Immunomodulation in Cancer and Regeneration, 23 June, 2017, Porto
- 6th edition of the Advanced Summer School - Interrogations at the Biointerface: Research/Clinical Interface at the Spine, June 19 - 22, 2017, Porto
- 24th International Symposium on Glycoconjugates, 27th August – 1st Sept, 2017; Jeju, South Korea. (http://glyco24.org/sub/catalog.php?CatNo=2; Member of the Scientific committee)
- Joint EpiChemBio and MuTaLig COST Actions Meeting, September 22 - 24, 2017, Porto (National Co-chair)
- 10th International Meeting of The Portuguese Society For Stem Cells and Cell Therapies (SPCE-TC), October, 12-14, 2017, Covilhã
- Fall Meeting of the EORTC / Endocrine Task Force 2017 & SPEDM, November 28,2017, Porto

MEMBERS AT EDITORIAL BOARDS OF SCIENTIFIC JOURNALS

- Advances in Anatomic Pathology
- American Journal of Cancer Therapy and Pharmacology
- Bioinspired, Biomimetic and Nanobiomaterials
- Biology
- BMC Cancer
- BMC Clinical Pathology
- Chromosome Research
- Clinical Epigenetics
- Computational Biology and Bioinformatics
- Current Diagnostic Pathology
- Dataset Papers in Biology
- Dataset Papers in Oncology
- Endocrine Pathology
- Endocrine Related Cancer
- European Journal of Cancer Prevention
- European Journal of Human Genetics
- Forensic Science International. Genetics
- Frontiers in Genetics
- Frontiers in Genomic Assay Technology
- Genes, Chromosomes and Cancer
- Helicobacter
- Histopathology
- International Journal of Medical Students
- International Journal of Surgical Pathology

- ISRN Genomics
- Journal of Applied Biomaterials & Functional Materials
- Journal of Biomedical Materials Research Part
- Journal of Clinical Pathology
- Journal of Integrated OMICS
- Journal of Materials Science: Materials in Medicine
- Journal of Pathology
- Molecules, Special Issue "Counteracting Drug Resistant Mechanisms in Cancer
- Open Pathology Journal
- Pathology, Research and Practice
- Patologia
- PeerJ
- PeerJ Computer Science Journals
- PloS one
- Regenerative Biomaterials
- Research in Cancer and Tumor
- Scandinavian Journal of Gastroenterology
- Scientific Reports
- Seminars in Diagnostic Pathology
- The Open Forensic Science Jounal
- The Scientific World Journal
- Ultrastructural Pathology
- Virchows Archiv: an International Journal of Pathology
- World Journal of Biological Chemistry
- World Journal of Clinical Infectious Diseases
- World Journal of Gastroenterology

16

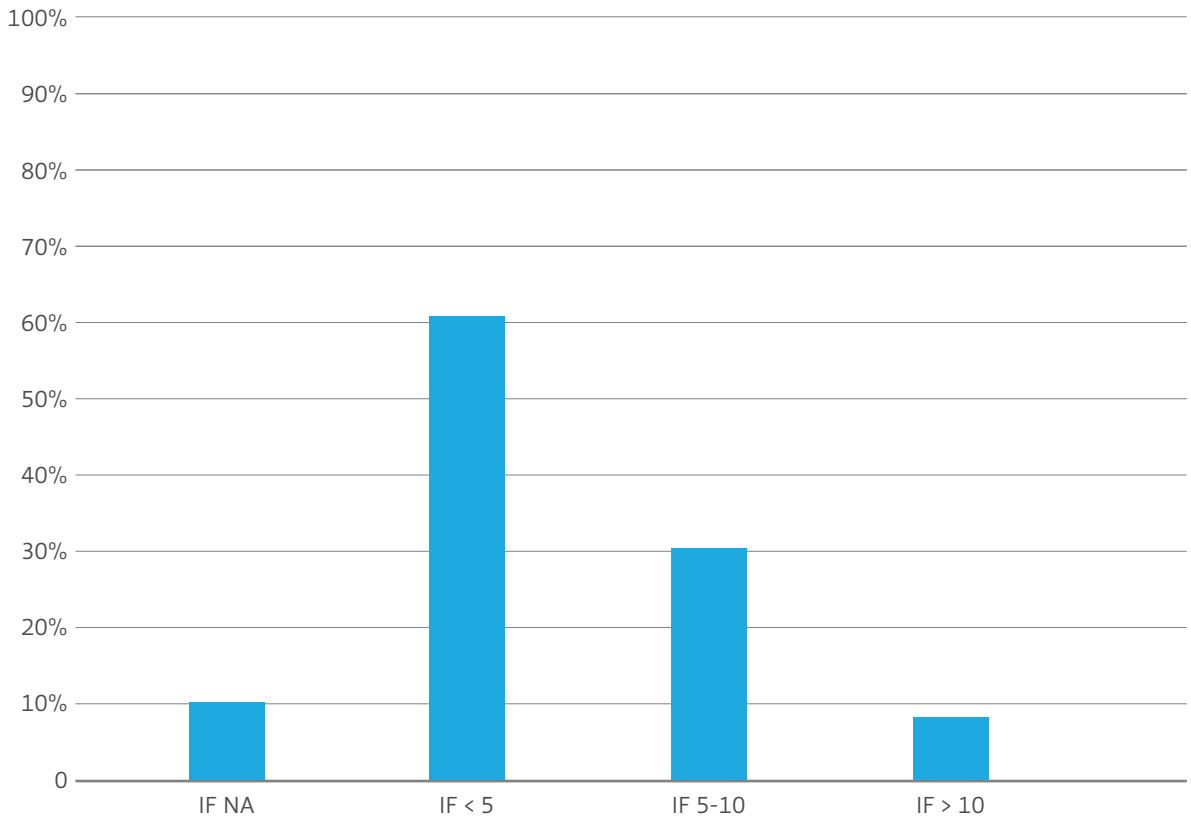
SCIENTIFIC PRODUCTION AT A GLANCE (2017)

Number of national patents	1
Number of international patents	0
Number of publications	511
Number of international peer-reviewed publications	460
Average Impact factor	5.254
Impact factor cumulative	2417.1
Number of publications with impact factor 5-10	110
Number of publications with impact factor > 10	39
Number of publications with impact factor > 10 with first or last author from the centre	18
Number of publications with impact factor > 10 co-authored by the centre	21
PhD Theses	23
MSc Dissertations	43

17

PERCENTAGE OF PUBLICATIONS ACCORDING WITH IMPACT FACTOR

Percentage of Publications according with Impact Factor



18

LIST OF PUBLICATIONS

1. Abreu, IM, Lau, E, de Sousa Pinto, B and Carvalho, D. Subclinical hypothyroidism: to treat or not to treat, that is the question! A systematic review with meta-analysis on lipid profile. Endocrine connections. 2017;6(3):188-99 https://www.ncbi.nlm.nih.gov/pubmed/28249936
2. Adaes, S, Almeida, L, Potes, CS, Ferreira, AR, Castro-Lopes, JM, Ferreira-Gomes, J and Neto, FL. Glial activation in the collagenase model of nociception associated with osteoarthritis. Mol Pain. 2017;13:1744806916688219 https://www.ncbi.nlm.nih.gov/pubmed/28326927
3. Afonso, O, Figueiredo, AC and Maiato, H. Late mitotic functions of Aurora kinases. Chromosoma. 2017;126(1):93-103 https://www.ncbi.nlm.nih.gov/pubmed/27106516
4. Akhmanova, A and Maiato, H. Closing the tubulin detyrosination cycle. Science. 2017;358(6369):1381-2 https://www.ncbi.nlm.nih.gov/pubmed/29242330
5. Albuquerque, A, Pessegueiro Miranda, H, Lopes, J, Gandara, J, Rodrigues, S, Gaspar, R, Morais, R, Ramalho, R, Rodrigues-Pinto, E, Cardoso, H, Barroca, H, Dias, CC, Carneiro, F and Macedo, G. Liver transplant recipients have a higher prevalence of anal squamous intraepithelial lesions. British journal of cancer. 2017;117(12):1761-7 https://www.ncbi.nlm.nih.gov/pubmed/29093575
6. Albuquerque, A, Rios, E and Macedo, G. The Impact of P16 Immunostaining in Reducing Anal Squamous Intraepithelial Lesions Indication for Treatment. Am J Surg Pathol. 2017;41(8):1151-2 https://www.ncbi.nlm.nih.gov/pubmed/28505001
7. Alexandre, N, Amorim, I, Caseiro, AR, Pereira, T, Alvites, R, Rema, A, Goncalves, A, Valadares, G, Costa, E, Santos-Silva, A, Rodrigues, M, Lopes, MA, Almeida, A, Santos, JD, Mauricio, AC and Luis, AL. Long term performance evaluation of small-diameter vascular grafts based on polyvinyl alcohol hydrogel and dextran and MSCs-based therapies using the ovine pre-clinical animal model. International journal of pharmaceutics. 2017;523(2):515-30 https://www.ncbi.nlm.nih.gov/pubmed/28283218
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Site, R, Biospecimen Core Resource, V, Brain Bank Repository-University of Miami Brain Endowment, B, Leidos Biomedical-Project, M, Study, E, Genome Browser Data, I, Visualization, EBI, Genome Browser Data, I, Visualization-Ucsc Genomics Institute, UoCSC, Chawla, A, Del Sal, G, Peltz, G, Brunet, A, Conrad, DF, Samuel, CE, O'Connell, MA, Walkley, CR, Nishikura, K and Li, JB. Dynamic landscape and regulation of RNA editing in mammals. Nature. 2017;550(7675):249-54
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GABINETE DE COMUNICAÇÃO E RELAÇÕES PÚBLICAS
T: +351 225 084 106
E-MAIL: gabinetedecomunicacao@ipoporto.min-saude.pt
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